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Embolic Diseases

Evolving Diagnostic and Management Approaches

Edited by Stanislaw P. Stawicki, Michael S. Firstenberg and Mamta Swaroop

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Meet the editors

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Mamta Swaroop, MD, FACS, FICS, FAIM, is an associate professor of surgery in the Division of Trauma and Critical Care and the Director for the Center for Global Surgery. She serves as the Global Surgery Program Director in the Feinberg School of Medicine at Northwestern University. Her lab, the Northwestern Trauma and Surgical Initiative (www.ntsi.global), aims to build sustainable access to surgical care through education and research in low resource settings, both locally and internationally. In 2018, she was honored as one of Oprah's Health Heroes, received the 39th annual Martin Luther King Humanitarian Award from Northwestern Memorial Hospital, presented the keynote address at the Royal College of Surgeons Global Frontiers Conference in London on the Bolivian Trauma Initiative, and held the first international TRUE

(Trauma Responders Unify to Empower) Communities Course. The Northwestern Trauma and Surgical Initiative (NTSI) conducts community-directed research and programmatic development in Southeast Asia, South America, and Chicago. Her work on helmet usage for female pillions on motorized two-wheelers added to work leading to legislative change in the governance of women needing to wear helmets in New Delhi. In Bolivia, her team writes and participates in legislation and implementation of a prehospital system. In Chicago, the TRUE Communities Course aims to empower communities to take action by turning bystanders into immediate responders. With more than 1500 people taught in Chicago, the course has spread to Mississippi and Bolivia, with revisions for London and Lagos. She has been an invited national and international visiting professor and keynote speaker, presenting on trauma and global surgery topics and has authored numerous peer-reviewed research articles. She is the co-editor of the book Success in Academic Surgery: Academic Global Surgery.

Contents

Foreword

Worldwide, there are nearly 250 million major surgical procedures performed annually. Despite generally excellent outcomes, associated health complications and consequences to individuals and health systems are significant. Within the overall subset of morbidity, embolic diseases feature very prominently. Such events range from the arterial to the venous emboli, from preoperative "incidental" findings to postoperative acute emergencies.

Embolic phenomena (EP) are known to affect key anatomical structures, from the brain to the heart, and can be present in a variety of settings, from pregnancy to war. In essence, emboli can be characterized as "non-stop concerns" and "sources of fear" for lay people and physicians alike. An embolism may be defined as the intravascular lodging of an embolus or vascular blockage-causing fragment, but it is not only that. An embolus is more than a fragment, it is a life-changing event for individuals and their families, and an economic burden to institutions, communities, industry, and governments. It is a round of biological consequences shot through society by Mother Nature. Consequently, the healthcare practitioner must not only be aware of diagnosis and treatment, but also understand the true global impact of EP from the perspectives of an individual patient, the health system, and the greater community.

My experiences in intensive care units run the gamut from very small institutions to well-recognized major medical centers, as well as those not only in the United States, but also in China, India, and Europe. I have also had the opportunity to participate in many local, national, and global public health efforts regarding community health problems and challenges, and while physicians and other healthcare providers may view emboli and embolism as a medical entity, they are also a public health problem with significant consequences. The authors of this text wish for you to know the nature and impact of emboli, and while the subject cannot be covered in its entirety from every aspect, the reader will be left better educated and with an indelible impression of the enormity of the problem.

This book provides a sampling of many of the problems encountered by healthcare providers in their day-to-day practice of medicine in regard to emboli. The overview provided by this text will be most valuable to those experienced in the care of patients as well as novices. The topics covered are of consequence to those in primary care as well as those who practice in the acute care or intensive care environments. The editors of this book have had considerable experience and involvement with the topics addressed, and have dedicated their professional lives to the care of the critically ill patient. Their choice of topics is to provide the healthcare provider with an overview of wide-ranging clinical situations to equip you, the reader, with tools to help the patient, and for you to better understand the ramifications of this pathology to society in general.

It is my hope that the examples provided to the reader in this important book will provide a solid clinical foundation in some of the vascular diagnoses that plague our patients, both in and out of the intensive care unit, and in the perioperative period. I commend the editors and individual chapter authors on their effort and product, and I believe that these materials will enhance patient care and outcomes, and expectantly assist in lessening the burden to families and the community.

Respectfully submitted,
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Preface

An embolism is defined as the intravascular lodging of an *embolus* or a *vascular blockage-causing fragment*. Emboli are a diverse group of pathological objects that travel within blood vessels, including blood clots or thromboemboli, air bubbles or *aeroembolism*, fat globules, infected particles or *septic emboli*, amniotic fluid or *amniotic emboli*, iatrogenically introduced foreign material like a catheter or wire fragments, and even bullet fragments and shrapnel. The most dreaded complication of an embolus is either partial or total blockage of blood flow distal to the site of embolization. This risk is inherent to the process of intravascular embolus migration, and can be controlled or limited only in cases where proper risk assessment—based on known predisposing factors—has been completed and appropriate therapeutic steps (e.g., anticoagulation, treatment of endocarditis) implemented.

Distal embolization can lead to limb, organ, and life-threatening sequelae of end-organ dysfunction, tissue ischemia, and potential necrosis. In cases of fat or amniotic fluid embolism, associated neurological sequelae may be devastating and severe. In fact, as a marker of the severity and complexity of the clinical problem, even in the absence of obvious neurologic findings, patients who present with a source of embolism, such as an intracardiac mass, often benefit from neurological imaging since many patients may have subclinical or *silent* strokes—a key clinical finding, critical in medical decision making, treatment, and risk stratification.

Although heterogeneous in their genesis, emboli often constitute a manifestation of other, concurrent pathological processes. For example, fat emboli are associated with long-bone fractures and surgical fixation. In another typical example, venous emboli may begin in the setting of trauma, malignancy, or various other hypercoagulable states. Arterial emboli, secondary to untreated atrial fibrillation, constitute a common emergency, leading to cerebrovascular infarcts and bowel and acute limb ischemia. Less common, but not less concerning, are left ventricular clots, often resulting from apical wall-motion abnormalities related to a previous myocardial infarction, which may present in a similar fashion.

Septic emboli originate from a variety of infectious foci, including endocarditis, prosthetic implants, soft tissue infections, and abscesses. If not recognized promptly, affected patients can suffer devastating systemic and neurological sequelae. Air emboli are most often iatrogenically induced. Due to their rarity, providers who are more likely to encounter air emboli in their practices must remain vigilant whenever in a situation prone to these uncommon phenomena. Foreign body emboli, whether iatrogenic or traumatic, constitute an acquired group of conditions. A phenomenon that is becoming better understood is the concept of a *paradoxical* embolism in which a venous source, such as a deep vein thrombosis, migrates across an intracardiac shunt or arteriovenous malformation and enters into the systemic, arterial, circulation. As such, whenever cases of paradoxical embolism are encountered, a search for venous-to-arterial shunting should be pursued and factored into the next steps. Finally, amniotic fluid embolism—one of the most devastating and poorly understood embolic phenomena—continues to be

associated with prohibitively high morbidity and mortality. Consequences of such occurrences can be truly catastrophic, with both short-term and long-term impacts on the patient and her family.

Many of the salient points emphasized throughout this book reflect the ongoing challenges and frustrations experienced by frontline clinicians. When embolic complications emerge, management is focused on treating the complication. The editors would like to emphasize how critical it is to identify and address the causative factors. Once a source of the embolus (or emboli) is identified, options for treatment are caged in discussions regarding the risks and benefits of various therapeutic options. When potential sources of embolisms are identified in the course of imaging for other reasons, discussions regarding clinical management are much more complicated—the decision to intervene, often with potentially high-risk treatments, on an asymptomatic patient cannot be taken lightly in the setting of the significant, and often life-long, implications of therapy in the context of the unknown risks for watchful waiting and hoping that a devastating embolic complication does not evolve or recur.

While our knowledge and scientific data on some causative pathologies is well established, many cases are nuanced and complicated not only by clinical manifestations of embolism but also by the inability to safely obtain a "tissue diagnosis" or ascertain greater diagnostic certainty. Consequently, in most instances both evaluation and treatment must be highly individualized. It is crucial to understand that therapies for *very similar problems can often be very different based upon patient risk factors and comorbidities*. For example, the management of a pulmonary embolism from a deep vein thrombosis after an orthopedic procedure is substantially different than a similar embolism in a patient with a known or newly diagnosed hypercoagulable state—such as lupus or an antiphospholipid antibody syndrome. A treatment plan for a young patient with a fat embolism following orthopedic surgery without any neurologic sequelae will be very different than the management of a young woman with an amniotic embolism who suffered from massive bilateral hemispheric strokes. Both patients will require highly individualized approaches, although their care will likely involve longer-than-expected hospital stays with a requirement for intensive care unit admission.

The primary goal of this book is to provide an overview of the most common types of embolic phenomena encountered in clinical practice, including certain key diagnostic and therapeutic considerations. Among the topics featured in the current collection are highly pertinent, up-to-date contributions in the areas of pulmonary embolism, fat embolism, embolic complications of non-malignant cardiac tumors, acute arterial embolism in the lower extremity, thrombophilia in pregnancy, bullet and shrapnel embolization, coronary artery embolization, as well as a comprehensive review of certain interventions utilized in the management of thromboembolic disorders.

When measured in terms of both human and financial costs, broadly defined *embolic phenomena* have a tremendous impact on individual patients, healthcare systems, and society around the globe. The introductory chapter provides a powerful overview of both economic and non-economic impacts of various types of embolism. Through our collaborative academic effort, of both the editorial team and the individual chapter authors, we hope to provide the reader with a valuable resource and a meaningful new insight into the gravity of the collective problem. Among other salient takeaway points is the ongoing dilemma of diagnostic relativity

and frequent uncertainty when managing embolic complications. Consequently, much more progress is required before any sort of "clinical victory" is declared in this important area of medicine and surgery.

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Chapter 1

Introductory Chapter: Defining the True Global Impact of Embolic Phenomena

Samantha Wolfe, Stanislaw P. Stawicki, Mamta Swaroop, Jennifer C.B. Irick and Michael S. Firstenberg

1. Introduction

In the realm of medical practice, the word "embolism" has many implications to many people [1, 2], with most providers instinctively placing this word within a negative context [3–5]. Derived from the Greek word, ἐμβολισμός, this term most literally means "interposition" [6]. Yet regardless of how benign the etymology may be, the clinical context is quite the opposite—synonymous with much dreaded morbidity and mortality [1, 2, 7–10]. Whether the embolus consists of a blood clot [8], a fat globule [11], a bubble of gas [12], amniotic fluid [9, 10], or even an iatrogenic or traumatic foreign body [13, 14], the unfavorable connotations persist even if the patient has few or no associated symptoms and requires no intervention.

The primary goal of this book is to provide the reader with an overview of the most common types of embolic phenomena encountered in clinical practice, including some of the key related diagnostic and therapeutic areas. The current collection of chapters includes important contributions in the areas of pulmonary embolism (PE), fat embolism (FE), embolic complications of nonmalignant cardiac tumors, acute arterial embolism (AAE) of the lower extremity, thrombophilia in pregnancy, bullet and shrapnel embolization (BSE), and coronary artery embolization (CAE), as well as a comprehensive chapter on venous interventions utilized in the management of thromboembolic disorders.

Perhaps the best way to paint the picture of the tremendous impact of "embolism" globally is to present the human costs and the resources required to treat various types, manifestations, and complications of embolic diseases. Although challenging to gather, such information was compiled by our team for the purposes of this introductory chapter and summarized in **Table 1** [12, 14–37]. Although far from comprehensive, we hope to provide the reader with valuable insight into the gravity of the collective problem.

2. Embolism types: a synopsis

No discussion of "embolism" can be complete without the discussion of risk factors, diagnostics including laboratory and imaging tests, and therapeutic considerations. Here, one must emphasize the importance of looking at the "totality of evidence," considering things like clinical suspicion, presence/absence of specific risk factors, positive/negative predictive values, diagnostic test sensitivity/specificity, and the pre–/posttest probabilities.

Embolism type (alphabetical) [Reference]	Number affected	Mortality	Morbidity	Healthcare costs	Other considerations
Air emboli [12, 15–18]	0.2–1% (with central line) 0.003–0.007% (cardiac bypass) Overall, 2.65 per 100,000 cases	14% 21.7%	Neurologic complications–encephalopathy to focal cerebral lesions (19–50%)	Legal: median payment $325,000/claim	ICU admission
Amniotic fluid [19, 20]	1/22,000 pregnancies Overall, 2–8/100,000 cases	10% of all maternal deaths 13–44% case maternal mortality 7–38% fetal mortality	Seizures (2.22%) Maternal neurologic damage (4.44%) Fetal neurologic damage (25–50%) Shock (15%) Coagulopathy (8.8%) Cardiac arrest (22.2%) Fetal NICU admission 8.8–20%	Prolonged hospitalization Average maternal LOS–2.92 days Average infant LOS–3.78 days	ICU admission Massive blood transfusion Long-term neurologic effects
Fat emboli [21–24]	Symptomatic: 1–20% patients with long bone fractures (true incidence is likely much higher)	5–15%	ARDS, pneumonia CVA Seizures, epilepsy (2.86%) DIC, thrombocytopenia (37%) Cardiac failure		ICU admission
Iatrogenic foreign body [14, 25–27]	Retained guidewire Approximately 1 in 3000 cases	<2% mortality	Cerebral ischemia Infarction Cardiac dysrhythmia, tamponade 5–32% symptomatic	Medicare: endovascular retrieval of foreign body—9.03 RVU which equates to $342.15 reimbursement Potential legal costs if foreign body not immediately recognized	Requirement for endovascular or operative removal
Peripheral emboli [28–30]	About 14 per 100,000 cases	17–18% death	Amputation (28.9%) Reperfusion injury (6%)		Requirement for fasciotomy, limb amputation, loss of function
Pulmonary embolism (PE) [31–37]	97.8 per 100,000 population/year (hospitalization rate)	0.1–4.2% in hospitalized patients ~25% at 7 days Up to 16% at 1 year	Bleeding related to thrombolytics and/or anticoagulants (4–7.5%) Right ventricular systolic dysfunction (20–60%)	Between $5,500 and $11,665 (depending on severity) with mean cost of $8800 $99,286/PE death (Cox)	Need for long-term anticoagulation Venous stasis Pulmonary hypertension Recurrent PE

ARDS = Acute respiratory distress syndrome; CVA = Cerebrovascular accident; DIC = Disseminated intravascular coagulation; ICU = Intensive care unit; LOS = Length of stay; NICU = Neonatal ICU; PE = Pulmonary embolism; RVU = Relative value unit.

Table 1.
Selected metrics demonstrating the global impact of embolic diseases, including considerations of both patient- and health system level considerations.

2.1 Pulmonary embolism

Initial clinical tests obtained when a patient exhibits symptoms of a PE are commonly electrocardiogram (EKG), arterial blood gas (ABG) analysis, and chest X-ray (CXR). However, none of these studies are sufficiently sensitive or specific for this diagnosis. Clinical scoring systems such as the Wells or PERC score have been established but in isolation are not able to diagnose PE [38]; rather, they provide clinically relevant risk stratification. Based on such risk stratification, it is recommended that a test of exclusion (e.g., one with a high negative predictive value) such as D-dimer be performed in the setting of low or intermediate clinical probability of a PE [39]. In the cases where a PE is highly suspected or likely, it is preferred to proceed directly to imaging such as a computed tomography pulmonary arteriography (CTPA). The ease of obtaining it, combined with the high predictive value (92–96%), has placed CTPA as the dominant imaging modality for suspected PE [40]. In patients unable to receive iodinated contrast, a ventilation-perfusion (V-Q) scan or a contrast-enhanced magnetic resonance angiography (MRA) may represent a valid alternative. MRA has a sensitivity of 78% and specificity of 99%. This imaging study, however, relies on patient participation and compliance, and therefore a nontrivial proportion of studies will be inadequate to obtain sufficient level of diagnostic accuracy [40]. Once diagnosed, the treatment of PE involves systemic anticoagulation, with more invasive measures such as thrombolysis or embolectomy performed in patients with significant hemodynamic instability, respiratory decompensation, or acute right ventricular dysfunction [37].

2.2 Fat emboli

Fat embolism syndrome (FES) differs in that there is no reliably accurate diagnostic or imaging test. Rather, the diagnosis is primarily clinical [11]. Multiple scoring systems exist which utilize the findings of petechiae, respiratory symptoms, fever, tachycardia, and radiographic changes with these either being identified as "major" or "minor" in magnitude or assigned a value on a pre-determined scale [11, 21, 41]. The lack of an imaging confirmatory test, however, makes it difficult to evaluate the true diagnostic accuracy or sensitivity of these indices. Ultrasound and echocardiography have been used to detect circulating fat globules; however, several studies suggest that a much higher percentage of patients with long bone fractures have circulating fat globules than previously thought, and only a fraction of these patients develop symptoms or FES [21, 42]. Computed tomography (CT) and magnetic resonance imaging (MRI) have been used, often with few abnormal findings reported. Treatment is mainly supportive and consists of intravenous fluids, respiratory support, and other forms of symptomatic management as appropriate. Medications such as steroids, heparin, alcohol, and dextran have not been proven beneficial [21].

2.3 Amniotic fluid embolism

Amniotic fluid embolism (AFE) is another condition that requires a high degree of clinical suspicion, as the diagnosis is based on a heterogeneous constellation of symptoms [9, 10]. AFE should be suspected in any case of sudden maternal cardiovascular collapse with accompanying coagulopathy, hypotension, seizures, or distress, with no other clearly identifiable cause [43–45]. There are currently no truly reliable laboratory tests that are diagnostic of AFE [46]. Detection of formed amniotic fluid components (epidermal squamous cells, meconium, or lanugo hairs) in the maternal pulmonary blood flow is sufficient for histologic diagnosis of AFE [20]. Unfortunately, in many cases AFE goes unrecognized until these findings are

Embolism type (alphabetical)	Risk factors
Air emboli [12, 16, 17, 48]	• Venous catheterization, removal, manipulation, unintended disconnection • CABG on CP bypass • Craniotomy, especially in sitting position • Fistulization between air filled viscus and vessel (aortoesophageal, atriobronchial) • Traumatic or iatrogenic pulmonary alveoli-venous fistula • PFO, VSD (for paradoxical air emboli) • Hemodialysis, cell saver transfusion
Amniotic fluid [19, 20]	• Multi-fetal pregnancy, placenta previa, placental abruption, eclampsia • Uterine rupture • Cell saver blood transfusion • Induction, C-section, fetal distress, cervical laceration/trauma, instrument delivery • Maternal age > 35 years
Fat emboli [24, 49, 50]	• Long bone fracture (pelvis, femur) • Joint arthroplasty • Percutaneous vertebroplasty • Liposuction, fat grafting • CABG • CPR • Organ transplant (lung, renal) • Bone marrow transplant or harvest • Chronic corticosteroid use • Severe burn
Iatrogenic foreign body [14]	• Guidewire–placement of central line, improper technique, or failure to control guidewire during procedure (more likely in emergency situations, inexperienced staff, inadequate supervision) • Catheter–fracture of catheter secondary to repetitive mechanical stress, damage during removal, and improper connection during placement • Coils–improperly sized or placed coils; tortuous vessels; usage of angioplasty balloon for deployment
Peripheral emboli [28–30]	• PFO in setting of venous thrombosis • Atrial fibrillation • History of central or peripheral atherosclerosis
Pulmonary embolism (PE) [51]	• Trauma • Prolonged hospitalization/immobility • Malignancy • Central venous catheterization, venous thrombosis, thrombophilia

CABG = Coronary artery bypass grafting; CP = Cardiopulmonary; CPR = Cardiopulmonary resuscitation; PFO = Patent foramen ovale; VSD = Ventricular septal defect.

Table 2.
Listing of the most common risk factors by embolism type.

seen on autopsy [9, 10]. Treatment is supportive, involving respiratory support, Cesarean section (if not already delivered), correction of coagulopathy, blood/blood product transfusion, vasopressors/inotropes, and fluids [9, 10, 43–45].

2.4 Air embolism

The most sensitive test for diagnosing an air embolism is the transesophageal echo (TEE), detecting as little as 0.02 ml/kg of air administered by bolus injection [12, 37]. In fact, it has been deemed almost "too sensitive," in that it will detect air in circulation that is not associated with any symptoms. A precordial Doppler is also highly sensitive, detecting as little as 0.25 ml of air (0.05 ml/kg) [37]. It is highly operator dependent, however, as one must rely on the detection of a change in sound with air interrupting the blood flow within the cardiac chambers. Much less sensitive is the pulmonary artery catheter, with a detection threshold of 0.25 mL/kg of air [47]. Additionally, it is of limited use therapeutically as its small caliber internal lumen is often insufficient to withdraw air from the chamber as a therapeutic maneuver (or at least quickly enough to be truly effective). In the operating room, the most practical diagnostic tool is a sudden fall in end-tidal CO_2, albeit this is highly nonspecific. Other times, air emboli will go undiagnosed by any formal means and may well end up being "presumed" based on clinical symptomatology presenting in a scenario where an air embolus is possible (**Table 2**).

2.5 Foreign body embolism

The method of detecting a foreign body embolus (FBE) is dependent on the resting intravascular location of the embolus, which may vary according to the etiology, object type, and route of introduction [13, 14, 52, 53]. For cardiac emboli, transesophageal echocardiography (TEE) is commonly used and is beneficial in that it can also assess for any structural damage associated with such FBEs [54]. This imaging modality may be limited, however, especially in instances when the emboli are small, minimally echogenic, located in difficult-to-access locations, or obscured by acoustic shadowing. In these cases, computed tomography (CT) imaging may represent a helpful adjunct to determine location and operative or endovascular plan for removal. CT angiography is also useful for more peripherally located FBEs [52, 53]. The decision on whether to remove the foreign body is also highly dependent on symptomatology and potential complications of the emboli, especially when considered in the context of any downstream anatomic structures as well as immediately surrounding tissues. In the current age, an endovascular approach is the most common, with open approaches often reserved for failure of endovascular retrieval. Rarely, an embolus may be left in place if it is unlikely to further migrate and the patient is asymptomatic, though this does leave the patient at potential risk for future complications that can occur remotely, even years later [13, 14, 55, 56].

3. Conclusion

Perhaps the most valuable take-away message of this book is that diagnostic relativity—rather than absolutism—continues to prevail in the realm of "embolic diseases." Such is the state of modern medical decision-making in this important area of active clinical investigation and management. **Table 2** summarizes the most common risk factors, organized by "embolism" type. Compiled from variety of sources, this information represents an good foundation for clinical discussions based on diagnostic probabilities.

In summary, this book represents a collection of contributions by a multidisciplinary team of clinicians and medical researchers. The editors' goal was to solicit the highest quality contributions from some of the top experts in their respective fields. We hope we were able to achieve this goal satisfactorily. Ultimately, the book's readers will be the best arbiters of its success, whether it is determined by the number of downloaded chapters or the cumulative number of citations attributable to this collection of chapters. To be able to contribute to the generation and dissemination of new knowledge in this important area of clinical investigation is a true privilege.

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References

[1] Nielsen HK et al. 178 fatal cases of pulmonary embolism in a medical department. Acta Medica Scandinavica. 1981;**209**(1-6):351-355

[2] Stawicki SP et al. Septic embolism in the intensive care unit. International Journal of Critical Illness and Injury Science. 2013;**3**(1):58

[3] Piqué-Angordans J, Posteguillo S. Peer positive and negative assessment in medical English written genres. Advances in medical discourse analysis: Oral and written. Contexts. 2006;**45**:383

[4] McCurdy T. Air-embolism complicating artificial pneumothorax: A case with autopsy. American Review of Tuberculosis. 1934;**30**(1):88-91

[5] Gross AF, Smith FA, Stern TA. Dread complications of catatonia: A case discussion and review of the literature. Primary Care Companion to the Journal of Clinical Psychiatry. 2008;**10**(2):153

[6] Wikipedia. Embolism. 2019. Available from: https://en.wikipedia.org/wiki/Embolism [Accessed: August 19, 2019]

[7] Ericsson JA, Gottlieb JD, Sweet RB. Closed-chest cardiac massage in the treatment of venous air embolism. New England Journal of Medicine. 1964;**270**(25):1353-1354

[8] Stawicki SP et al. Deep venous thrombosis and pulmonary embolism in trauma patients: An overstatement of the problem? The American Surgeon. 2005;**71**(5):387-391

[9] Thongrong C et al. Amniotic fluid embolism. International Journal of Critical Illness and Injury Science. 2013;**3**(1):51

[10] Balinger KJ et al. Amniotic fluid embolism: Despite progress, challenges remain. Current Opinion in Obstetrics and Gynecology. 2015;**27**(6):398-405

[11] Kwiatt ME, Seamon MJ. Fat embolism syndrome. International Journal of Critical Illness and Injury Science. 2013;**3**(1):64

[12] Gordy S, Rowell S. Vascular air embolism. International Journal of Critical Illness and Injury Science. 2013;**3**(1):73

[13] Moffatt-Bruce SD et al. Intravascular retained surgical items: A multicenter study of risk factors. Journal of Surgical Research. 2012;**178**(1):519-523

[14] Wojda TR et al. Foreign intravascular object embolization and migration: Bullets, catheters, wires, stents, filters, and more. In: Embolic Diseases: Unusual Therapies and Challenges. London, England: IntechOpen; 2017. 109p

[15] Bessereau J, Genotelle N, Chabbaut C, et al. Long-term outcome of iatrogenic gas embolism. Intensive Care Medicine. 2010;**36**(7):1180-1187

[16] Brull SJ, Prielipp RC. Vascular air embolism: A silent hazard to patient safety. Journal of Critical Care. 2017;**42**:255-263

[17] Pinho J, Amorim JM, Araujo JM, et al. Cerebral gas embolism associated with central venous catheter: Systematic review. Journal of the Neurological Sciences. 2016;**362**:160-164

[18] Hammon JW, Hines MH. Cardiac surgery in the adult. In: Cohn LH, editor. Extracorporeal Circulation. 4th ed. New York: McGraw-Hill; 2012

[19] Spiliopoulos M, Puri I, Jain NJ, et al. Amniotic fluid embolism-risk factors, maternal and neonatal outcomes. The

Journal of Maternal-Fetal & Neonatal Medicine. 2009;**22**(5):439-444

[20] Rath WH, Hofer S, Sinicina I. Amniotic fluid embolism: An interdisciplinary challenge: Epidemiology, diagnosis and treatment. Deutsches Ärzteblatt International. 2014;**111**(8):126

[21] Talbot M, Schemitsch EH. Fat embolism syndrome: History, definition, epidemiology. Injury. 2006;**37**(Suppl 4):S3-S7

[22] Habashi NM, Andrews PL, Scalea TM. Therapeutic aspects of fat embolism syndrome. Injury. 2006;**37**(Suppl 4):S68-S73

[23] Kavi T, Teklemariam E, Gaughan J, et al. Incidence of seizures in fat embolism syndrome over a 10-year period: Analysis of the national inpatient sample database. The Neurologist. 2019;**24**(3):84-86

[24] Kosova E, Bergmark B, Piazza G. Fat embolism syndrome. Circulation. 2015;**131**(3):317-320

[25] Vannucci A, Jeffcoat A, Ifune C, et al. Special article: Retained guidewires after intraoperative placement of central venous catheters. Anesthesia and Analgesia. 2013;**117**:102-108

[26] Schechter MA, O'Brien PJ, Cox MW. Retrieval of iatrogenic intravascular foreign bodies. Journal of Vascular Surgery. 2013;**57**:276-281

[27] Roddy SP. Endovascular foreign body retrieval. Journal of Vascular Surgery. 2013;**57**(2):599

[28] Costantini V, Lenti M. Treatment of acute occlusion of peripheral arteries. Thrombosis Research. 2002;**106**(6):V285-V294

[29] Aune S, Trippestad A. Operative mortality and long-term survival of patients operated on for acute lower limb ischaemia. European Journal of Vascular and Endovascular Surgery. 1998;**15**:143-146

[30] Fagundes C, Fuchs FD, Fagundes A, et al. Prognostic factors for amputation or death in patients submitted to vascular surgery for acute limb ischemia. Vascular Health and Risk Management. 2005;**1**(4):345

[31] Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: A population-based case-control study. Archives of Internal Medicine. 2010;**160**(6):809-815

[32] Cox CE, Carson SS, Biddle AK. Cost-effectiveness of ultrasound in preventing femoral venous catheter-associated pulmonary embolism. American Journal of Respiratory and Critical Care Medicine. 2003;**168**(12):1481-1487

[33] Kempny A et al. Incidence, mortality, and bleeding rates associated with pulmonary embolism in England between 1997 and 2015. International Journal of Cardiology. 2019;**277**:229-234

[34] Brennan P et al. Real World Outcomes for "Intermediate-High" Mortality Risk Patients Presenting with Submassive Pulmonary Embolism in a Tertiary Cardiothoracic Centre. London, United Kingdom: BMJ Publishing Group Ltd and British Cardiovascular Society; 2019

[35] Fanikos J et al. Hospital costs of acute pulmonary embolism. The American Journal of Medicine. 2013;**126**(2):127-132

[36] Dismuke SE, Wagner EH. Pulmonary embolism as a cause of death: The changing mortality in hospitalized patients. JAMA. 1986;**255**(15):2039-2042

[37] Jaff M, McMurty MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: A scientific statement from the American Heart Association. Circulation. 2011;**123**(16):1788-1830

[38] Stawicki SP et al. Transthoracic echocardiography for suspected pulmonary embolism in the intensive care unit: Unjustly underused or rightfully ignored? Journal of Clinical Ultrasound. 2008;**36**(5):291-302

[39] Stein PD, Woodard PK, Weg JG, et al. Diagnostic pathways in acute pulmonary embolism: Recommendations of the PIOPEDII investigators. Radiology. 2007;**242**(1):15-21

[40] Sherk WM, Stojanovska J. Role of clinical decision tools in the diagnosis of pulmonary embolism. American Journal of Roentgenology. 2017;**208**(3):W60-W70

[41] Shaikh N. Emergency management of fat embolism syndrome. Journal of Emergencies, Trauma, and Shock. 2009;**2**(1):29

[42] Eriksson EA, Pellegrini DC, Vanderkolk WE, et al. Incidence of pulmonary fat embolism at autopsy: An undiagnosed epidemic. Journal of Trauma and Acute Care Surgery. 2011;**71**(2):312-315

[43] Clark SL. Amniotic fluid embolism. Obstetrics & Gynecology. 2014;**123**(2):337-348

[44] Killam A. Amniotic fluid embolism. Clinical Obstetrics and Gynecology. 1985;**28**(1):32-36

[45] Pacheco LD et al. Amniotic fluid embolism: Diagnosis and management. American Journal of Obstetrics and Gynecology. 2016;**215**(2):B16-B24

[46] Stawicki SP, Papadimos TJ. Challenges in managing amniotic fluid embolism: An up-to-date perspective on diagnostic testing with focus on novel biomarkers and avenues for future research. Current Pharmaceutical Biotechnology. 2013;**14**(**14**):1168-1178

[47] Mirski MA, Lele AV, Fitzsimmons L, et al. Diagnosis and treatment of vascular air embolism. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2007;**106**(1):164-177

[48] Brook OR, Hirshenbaum A, Talor E, et al. Arterial air emboli on computed tomography (CT) autopsy. Injury. 2012;**43**(9):1556-1561

[49] Morales-Vidal SG. Neurologic complications of fat embolism syndrome. Current Neurology and Neuroscience Reports. 2019;**19**(3):14

[50] Molière S, Kremer S, Bierry G. Case 254: Posttraumatic migrating fat embolus causing fat emboli syndrome. Radiology. 2018;**287**(3):1073-1080

[51] Bělohlávek J, Dytrych V, Linhart A. Pulmonary embolism, part I: Epidemiology, risk factors, and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. Experimental and Clinical Cardiology. 2013;**18**(2):129

[52] Huebner S, Ali S. Bilateral shotgun pellet pulmonary emboli. Journal of Radiology Case Reports. 2012;**6**(4):1

[53] Bach AG et al. Imaging of nonthrombotic pulmonary embolism: Biological materials, nonbiological materials, and foreign bodies. European Journal of Radiology. 2013;**82**(3):e120-e141

[54] Herbert JT, Kertai MD. Transesophageal echocardiography use in diagnosis and management of

embolized intravascular foreign bodies. In: Seminars in Cardiothoracic and Vascular Anesthesia. Los Angeles, CA: SAGE Publications Sage CA; 2018

[55] Elison RMA et al. Surgical management of late bullet embolization from the abdomen to the right ventricle: Case report. International Journal of Surgery Case Reports. 2017;**39**:317-320

[56] Adegboyega PA, Sustento-Reodica N, Adesokan A. Arterial bullet embolism resulting in delayed vascular insufficiency: A rationale for mandatory extraction. Journal of Trauma and Acute Care Surgery. 1996;**41**(3):539-541

Chapter 2

Fat Embolism: What We Have Learned from Animal Models

Alan M. Poisner and Agostino Molteni

Abstract

Pulmonary fat embolism may not be diagnosed before unrelated autopsy and have little clinical impact or lead to acute lung injury with fulminant fat embolism syndrome (FES). The fat may come from various anatomic locations, bone marrow being the most common. There is no specific treatment. This review discusses animal models that can lead to a better understanding of pathophysiological mechanisms underlying this condition and indicates the importance of specific cellular constituents. A hypothesis is postulated that there is a vicious cycle involving oleic acid and angiotensin II (both of which are pulmonary toxicants): oleic acid is derived from lipid embolism by pulmonary lipases that are stimulated by angiotensin; oleic acid also promotes local generation of angiotensin. The potential role of fatty acid receptors and the resolution of this cycle are discussed. Studies show there is potential for long-term effects that might not be revealed in the immediate post-recovery period. Evidence is reviewed that animals are vulnerable to "second hit" effects at a time remote from the initial event. Some beneficial pharmacological treatments are described. These include different drugs acting on the renin-angiotensin system (RAS) that could eventually serve alone or in combination for treatment or prevention. Future therapeutic developments are discussed.

Keywords: fat embolism, lung, renin-angiotensin system, rat, drug treatment, time course, second hit, animal model, histopathology, triolein

1. Introduction

Fat embolism was described many years ago. As early as 1862 [1] as cited in a 1971 review by Herndon [2], there was a report of fat droplets in the lungs of a factory worker who died after a crushing injury to his chest and abdomen. The term "fat embolism" itself includes many types of conditions in which some type of fatty substance is embedded in a tissue remote from its source. The most common source is from bone marrow that escapes into the venous system after trauma and surgery, including bone marrow reaming [3], liposuction [4], fat injection [5], or necrosis, as in sickle cell disease resulting in acute chest syndrome [6]. There are also some forms that do not result from trauma or surgery [7]. What distinguishes fat embolism from other strictly physical forms is that in addition to the physical obstruction of the vasculature that can accompany the lodging in capillaries, there are also biochemical consequences in response to the ensuing lipid metabolism and also pathological processes that are triggered intracellularly after engulfing of the fat. The most common target for embolic fat is the lung, but other significant sites include the skin, the eyes, and the brain with subsequent clinical sequelae [8].

The clinical consequences of fat embolism have been reviewed many times over the years, including this year [8]. The symptoms may be so minor that they can be missed [9] or appear after an interval as much as 48–96 h leading to acute respiratory distress syndrome [ARDS] with mortality ranging from 10 to 15% [8, 9]. This has been called fat embolism syndrome [FES], sometimes with accompanying CNS [10], ocular [11] or dermal pathology [12]. Treatment has been supportive: recent reviews indicate that there is no specific treatment available [8, 12]. Although a patent foramen ovale is sometimes a contributing factor in systemic consequences of fat embolism, for instance, in the eye and the brain, this is clearly not the case in most cases of FES.

Therefore, there have been many attempts to produce an animal model in hopes of delineating the underlying pathophysiology, so specific treatment could be obtained. Animal models have included rats [13], mice [14], rabbits [15], dogs [16], sheep [17], pigs [18], and even baboons [19]. While a majority of these studies have focused on orthopedic-related problems [20], it would help to examine a wide variety of initiating causes in order to find some common underlying pathophysiological processes. This might lead to more specific methods to treat or prevent this condition before the array of downstream mediators, such as peptides and cytokines, have been activated. The aim of this chapter is to review what has been learned from the diverse animal studies and provide one unifying concept based on the role of the renin-angiotensin system as a key player in fat embolism syndrome.

2. Studies on bone

2.1 Reaming and nailing

In order to simulate in animals the surgical procedure used in humans that can lead to fat embolism syndrome, a number of different animals have been subjected to nailing, with or without reaming [3]. It was concluded that more experiments should be carried out in order to determine the optimal method to perform the surgical procedures. It was also made clear that other factors influence the development of systemic and pulmonary complications [3]. A comprehensive review of animal studies of intramedullary nailing concludes that events that may predispose to adverse postsurgical impact are important and that studies should take these into consideration [20].

2.2 Bone marrow fat and non-bone marrow fat injection

A number of studies have been carried out with infusions of bone marrow extracts or non-marrow fat. An excellent review on animal studies of acute lung injury, which includes oleic acid as a possible model for fat embolism, indicates that this model does not really mimic the clinical syndrome of FES [21]. In addition, a study on rats showed that the intravenous injection of oleic acid, unlike neutral fat, did not result in the deposition of fat droplets [22].

A study on liposuction in rats performed on the lateral flank and the abdomen showed that fat was delivered to the lungs and other organs [23]. Some animal studies on fat embolism have utilized subcutaneous fat [22]. This has clinical parallels in which subcutaneous injection in humans has caused fatal fat embolism [24].

3. Triolein: the prototype fat embolism model

Since neutral fat seems to be the main culprit in fat embolism and is the major fat in bone marrow and subcutaneous tissues [25] and pulmonary emboli [26], the

neutral fat triolein has been the most studied in vivo and in vitro. Although a number species have been studied, the rat has been studied the most, particularly after the groundbreaking work of L.F. Peltier [27–29]. He studied fat embolism in cats and dogs but mostly in rats. This work included description of the fat content of bone marrow and body fat, distribution of labeled triolein after i.v. injection, changes in blood and lung lipase after embolism, kinetics of the phenomena, and other studies in animals and patients. Some advantages of triolein studies in the rat are described below.

3.1 Advantages of triolein and our model

Triolein [glyceryl trioleate] is available as a pure liquid that can be injected i.v. directly or after emulsification. We have used conscious animals since there are studies indicating that anesthesia alters pulmonary response to fat embolism [30]. Although oleic acid is a well-known pulmonary toxicant, as mentioned above, it is not a suitable model for fat embolism syndrome. The conversion of triolein to oleic acid by pulmonary tissue [31] provides support for the proposed sequence of events postulated by Szabo [32].

3.2 Findings in the conscious rat triolein model of fat embolism

3.2.1 Time course of changes in pulmonary histopathology

Initial histopathological studies on the time course of triolein-induced lung injury revealed changes as early as 12–24 h which included thickening of the arterial and arteriolar media, mostly with myofibroblasts and inflammation in the septa with increased numbers of macrophages. Bronchial alveolar lavage (BAL) at 24 h revealed macrophages, some of which showed inflammatory response and fat droplets. Inflammation was still present at 11 days with damage to the bronchial epithelium [33].

Later studies at 3 and 6 weeks showed that after the first peak [48–72 h] and partial resolution, there were persistent and progressive inflammatory and fibrotic changes up to 6 weeks after injection of triolein [34]. This was associated with an increase in angiotensin peptides [34], implicating the renin-angiotensin system (RAS) in the pathophysiology (see below).

In order to determine if the lungs of the animals at this late time would be especially sensitive to another pulmonary insult, the animals were exposed to the known pulmonary toxicant lipopolysaccharide (LPS) at 6 weeks. Forty-eight hours after this "second hit," there was an enhanced histopathological response in animals previously exposed to triolein [35].

These animals had apparently recovered completely at 6 weeks from the initial triolein treatment as judged by normal weight gain and no observable behavioral changes. It was concluded that the compromised lungs seen at 6 weeks exposed the vulnerability of animals long after they had seemingly recovered. The histopathology was also found at 10 weeks along with the persistence of some small fat droplets extracellularly and also in some macrophages [36] [see below].

4. Role of the renin-angiotensin system

Because the renin-angiotensin system (RAS) has been implicated in a wide variety of other pulmonary experimental models [37, 38], we examined whether this might hold true for the fat embolism model, and in fact it has since been proposed that most forms of pulmonary inflammatory disease involve the RAS, but that list did not include fat embolism [39]. We found that three different agents that interfere

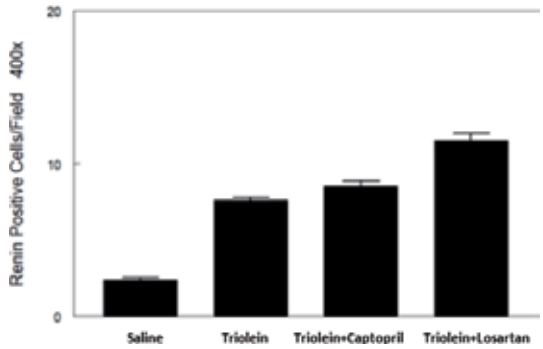

Figure 1.
Triolein increases lung renin staining: enhanced by captopril and losartan [64].

with the RAS were found to ameliorate the pulmonary damage found at 48 h after triolein: the angiotensin-converting enzyme (ACE) inhibitor captopril [40], the angiotensin II type 1 receptor blocker losartan [40], and the renin inhibitor aliskiren [41]. In addition, it was found that the remaining inflammation that was evident at 6 weeks was also reduced when losartan was given at this late time period and the animals were sacrificed 4 weeks later (10 weeks after the initial exposure to triolein) [36]. These results suggest that angiotensin II, produced by the angiotensin-converting enzyme (ACE) and acting on the type 1 receptor, is a critical pathological actor in the pathophysiology of fat embolism both acutely and after a substantial delay. However, it does not indicate precisely where this peptide comes from or how it is formed. All of the components of the RAS have been found or implicated in the lung [42]. Possible players in its formation prior to ACE activity could be renin or prorenin that is catalytically active when bound to its receptor [43]. Furthermore, other angiotensin peptides with anti-inflammatory and antifibrotic activity could be counterbalancing forces as well. Most of the extrarenal renin is in the form of prorenin which also has angiotensin-independent pro-fibrotic properties [44–46].

There are many possible cells that could provide components of the RAS to the pulmonary inflammatory process. These include mast cells [47], fibroblasts [48], myofibroblasts [49], vascular smooth muscle [50], and macrophages [51].

There are a number of studies suggesting a critical role of mast cells in RAS mediation of pulmonary pathology [52–54]. It has been suggested that activated macrophages stimulate pulmonary mast cells to release renin and the subsequent production of angiotensin peptides leads to adverse reactions [54]. Mast cells have also been shown to stimulate fibroblasts in the lung [55]. Triolein increases mast cell accumulation in a chronic model, and their appearance is reduced by losartan [56], and aliskiren reduces the triolein-induced increase of mast cell number found at 48 hours [57]. Another mast cell enzyme that has been implicated in angiotensin formation is chymase [58, 59]. It is known that there is mast cell heterogeneity in rodents and humans [60–62], and in humans this includes the presence of renin and its localization within the lungs [62].

In support of the importance of renin/prorenin in fat embolism, we have found an increase in renin staining at 48 hours (**Figure 1**) and 6 weeks after triolein-induced fat embolism [63, 64].

5. The nexus of fat metabolism and action and the RAS in the lungs

It has long been speculated that angiotensin II, acting through the type 1 receptor, was a primary inflammatory molecule [65]. In recent years it has become apparent that angiotensin II acting through its type 2 receptor has anti-inflammatory

actions [66] and the literature on similar anti-inflammatory actions through the Ang 1-7/Mas receptor have exploded [67]. It appears that the pathophysiological state of the lungs is a balance between the pro-inflammatory, pro-fibrotic arm of the RAS, and the counterbalancing peptide/receptor activity. It is not surprising that Ang 1-7 has been found to have beneficial effects in the lung [68, 69].

How is the renin-angiotensin system activated in fat embolism, and what is the connection to fat (neutral and fatty acids)? One suggestion based on the work of Gonzalez et al. [52, 54, 70] would have a sequence of fat engulfment by macrophages, and subsequently the activated cells would release monocyte chemoattractant-1 (MCP-1) that stimulates mast cells (nearby or remote) to release renin and angiotensin generation. However, activated macrophages themselves might act in an autocrine or paracrine manner to release renin, and there is evidence for intracrine generation of angiotensin as well [71, 72]. There may be intracrine actions of angiotensin as well on mitochondria and nuclei.

If the RAS is involved in many aspects, including initiating a cascade of downstream malevolent molecules, where does the fat enter the picture? As a host of review articles have discussed, there is a strictly mechanical phase during which the fat emboli obstruct capillaries and cause a short-term hypoxia. It is known that hypoxia itself can lead to pulmonary dysfunction and this can be offset experimentally by angiotensin-converting enzyme inhibition (ACEI) [73] and is associated with an increase in circulating angiotensin peptides [74].

It is clear from the vast literature on metabolism of fat after embolism that most of the lipolysis of neutral fat (mostly triolein) takes place near pulmonary endothelial cells that convert triolein to the toxic oleic acid by lipoprotein lipase. It is now known that oleic acid, although not thought to enter cells [21], can activate its own fatty acid receptor (FFAR/GPR120) which can evoke pulmonary edema [75, 76]. Interestingly, the toxic effects of oleic acid (including pulmonary edema) are antagonized by the non-specific angiotensin receptor blocker 1-sarcosine, 8-isoleucine angiotensin II [77]. This implicates angiotensin II in another way as a key mediatory in pulmonary pathology. It has also been reported that oleic acid and angiotensin II are synergistic in promoting a mitogenic effect in vascular smooth muscle [78]. Oleic acid emanating from triolein thus is a co-conspirator in evoking pulmonary (and probably other) pathological conditions, such as cerebral fat embolism [10, 79]. Pathways that oleic acid and angiotensin utilize in producing pathological responses are listed in **Figure 2**.

5.1 A vicious cycle of oleic acid and angiotensin II in fat embolism syndrome

To explain how the sudden appearance of fat in the pulmonary circulation can sometimes produce an acute respiratory distress syndrome and why the neutral fat (primarily triolein) has the potential to lead to longer-term pulmonary damage, the following hypothesis is presented (**Figure 3**). The initial mechanical phase of vascular obstruction which leads to hypoxia is known to be ameliorated by the angiotensin receptor blocker losartan [80].

The delayed metabolic phase is related to breakdown of the most abundant fat in emboli which is hydrolyzed by several triglyceride lipases to yield oleic acid. These include endothelial lipase (EL) and lipoprotein lipase (LIPL) [81, 82] as well as macrophage LIPL [83]. This in turn leads to the evolution of free fatty acids, mainly oleic acid, which is toxic to the endothelium and is released in part in close proximity to endothelial cells. Macrophages become activated after phagocytosing lipid particles which leads to paracrine and endocrine activation of mast cells that induces angiotensin generation [54].

In addition, there is generation of angiotensin and oleic acid intracellularly in macrophages (both of which are toxic to mitochondria [84, 85]). Since oleic acid

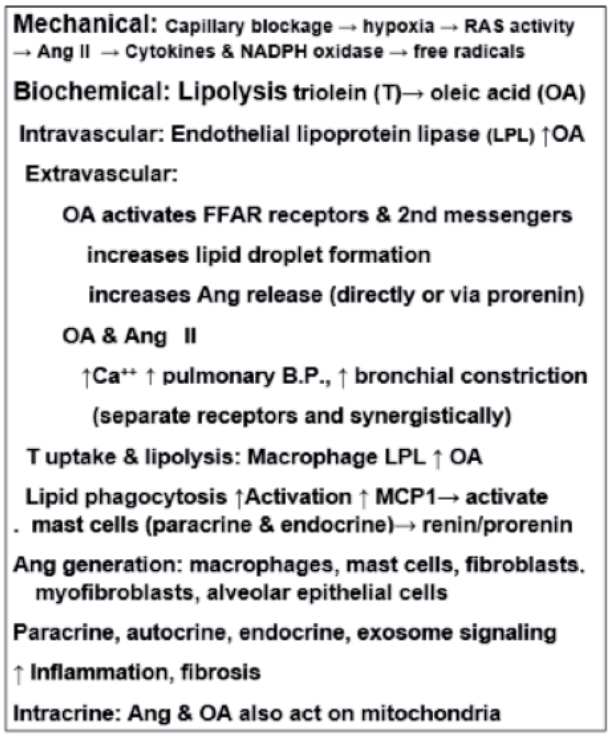

Figure 2.
Fat embolism pathways.

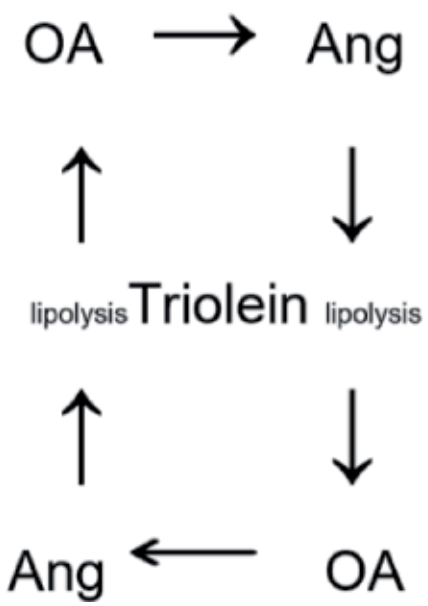

Figure 3.
Oleic acid-angiotensin cycle: OA ↑ Ang release; Ang ↑ triolein lipolysis.

has been shown to increase angiotensin II release from several cell types [86] and angiotensin increases the expression of various lipases [87], the cycle continues until rescue mechanisms ensue (**Figure 4**). It should be noted that losartan and perindopril, ACE inhibitors, prevent fatty acid-induced endothelial dysfunction

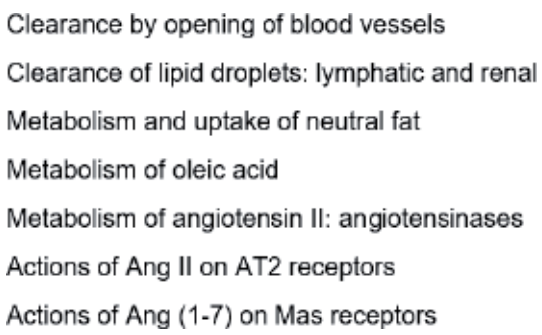

Figure 4.
Repair mechanisms for fat embolism.

in humans in response to elevated blood lipids [88]. Furthermore, oleic acid also increases serum renin and angiotensin, and its effects on pulmonary edema are blocked by blocked by an ACE inhibitor [89].

Most cases of fat embolism do not lead to fat embolism syndrome because the amount of the fat is not of sufficient volume or due to the countervailing mechanisms. These include actions of angiotensin II on AT2 receptors, metabolism of angiotensin II by angiotensinases, anti-inflammatory actions of its metabolite, angiotensin (1-7), metabolism of oleic acid, clearance of lipids via vascular or lymphatic channels, and ultimately renal excretion (**Figure 4**).

6. Conclusions and prospects

It is proposed that elements of the renin-angiotensin system are central mediators of tissue injury after fat embolism. Although hypoxia due to capillary blockage is a contributing factor to lung injury, oleic acid liberated from triolein hydrolysis is a crucial step, and it also is associated with angiotensin biology. Angiotensin II through its type 1 receptor is the major offender. Our animal experiments have indicated that three US Food and Drug Administration (FDA)-approved drugs (captopril, losartan, and aliskiren) may have protective value as mentioned above. However, in a clinical setting where trauma or surgery may be involved, stability of blood pressure may be compromised by these agents. Therefore, it is suggested that some of these types of agents (or a combination) could be administered by inhalation.

Rather than antagonizing the angiotensin II generation with ACE or renin inhibitors or angiotensin type 1 activity with antagonists (ARBS), it may be possible to treat/prevent fat embolism injury by stimulating the angiotensin type 2 receptor (AT2) with peptide or non-peptide agonists such as C21 [90]. Another possible therapeutic approach would be to activate the ACE2/angiotensin [1-7]/MAS axis with a peptide or non-peptide agonist, such as AVE0091 [68]. A more promising avenue for preventing or treating fat embolism will more likely be satisfactory if multiple points of the early stages of the pathophysiology are attacked simultaneously. That would include not only the RAS drugs mentioned above but also possibly mast stabilizers that can be given by the inhalation route and some of the newly described drugs that act on the FFA receptors mentioned above. In addition it is possible that some of the newer triglyceride lipase inhibitors could be of value as preventive treatment.

Although the emphasis in this review is on pulmonary fat embolism, there is ample evidence from clinical experience and animal experiments that the eyes, particularly the retina, are frequently targets of fat embolism. Both triolein and oleic acid have been implicated in ocular pathology [91, 92], and the RAS is thought to be an important mediating system in many ocular diseases [93].

Another non-pulmonary target of fat embolism in clinical FES is the brain, and cerebral fat embolism can be fatal [94]. Although a patent foramen ovale is sometimes an important factor in cerebral fat embolism, this is clearly not the case in many instances, and animal models have not provided any new insights of cardiac defects being major players. In a rat model, there is some evidence that cerebral fat embolism may involve a serine protease [79] and maybe this could be related to a non-renin generation of angiotensin by a chymase-like enzyme. The RAS is now believed to be important for much CNS pathology [95].

There now is reason to be optimistic that the next comprehensive review of fat embolism syndrome will describe some new available therapeutic options based on animal experiments. This reinforces the goal of animal experiments to delineate the pathophysiological mechanisms underlying human disease, so specific treatment can be implemented.

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References

[1] Zenker FA. Beiträge zur normalen und pathologischen Anatomie der Lungen. Braunsnsdorf: Dresden; 1862

[2] Herndon JH, Riseborough EJ, Fischer JE. Fat embolism: A review of current concepts. The Journal of Trauma. 1971;**11**(8):673-680

[3] Hildebrand F, Andruszkow H, Barkatali BM, Pfeifer R, Lichte P, Kobbe P, et al. Animal models to assess the local and systemic effects of nailing: Review of the literature and considerations for future studies. Journal of Trauma and Acute Care Surgery. 2014;**76**(6):1495-1506

[4] Cantu CA, Pavlisko EN. Liposuction-induced fat embolism syndrome: A brief review and postmortem diagnostic approach. Archives of Pathology & Laboratory Medicine. 2018;**142**(7):871-875

[5] Cardenas-Camarena L, Bayter JE, Aguirre-Serrano H, Cuenca-Pardo J. Deaths caused by gluteal lipoinjection: What are we doing wrong? Plastic and Reconstructive Surgery. 2015;**136**(1):58-66

[6] Vichinsky E, Williams R, Das M, Earles AN, Lewis N, Adler A, et al. Pulmonary fat embolism: A distinct cause of severe acute chest syndrome in sickle cell anemia. Blood. 1994;**83**(11):3107-3112

[7] Schulz F, Trubner K, Hildebrand E. Fatal fat embolism in acute hepatic necrosis with associated fatty liver. The American Journal of Forensic Medicine and Pathology. 1996;**17**(3):264-268

[8] Fukumoto LE, Fukumoto KD. Fat embolism syndrome. The Nursing Clinics of North America. 2018;**53**(3):335-347

[9] Eriksson EA, Pellegrini DC, Vanderkolk WE, Minshall CT, Fakhry SM, Cohle SD. Incidence of pulmonary fat embolism at autopsy: An undiagnosed epidemic. Journal of Trauma. 2011;**71**(2):312-315

[10] Dines DE, Burgher LW, Okazaki H. The clinical and pathologic correlation of fat embolism syndrome. Mayo Clinic Proceedings. 1975;**50**(7):407-411

[11] Spirn MJ, Biousse V. Retinal fat emboli. The Journal of Emergency Medicine. 2005;**29**(3):339-340

[12] Shaikh N. Emergency management of fat embolism syndrome. Journal of Emergencies, Trauma, and Shock. 2009;**2**(1):29-33

[13] Inoue H, Hanagama M, Kamiya M, Shinone K, Nata M. Experimental pulmonary fat embolism induced by injection of triolein in rats. Legal Medicine. 2008;**10**:26-30

[14] Zhang Y, Tian K, Wang Y, Zhang R, Shang J, Jiang W, et al. The effects of aquaporin-1 in pulmonary edema induced by fat embolism syndrome. International Journal of Molecular Sciences. 2016;**17**(7):1183

[15] Woo OH, Yong HS, Oh YW, Shin BK, Kim HK, Kang EY. Experimental pulmonary fat embolism: Computed tomography and pathologic findings of the sequential changes. Journal of Korean Medical Science. 2008;**23**(4):691-699

[16] Byrick RJ, Mullen JB, Mazer CD, Guest CB. Transpulmonary systemic fat embolism. Studies in mongrel dogs after cemented arthroplasty. American Journal of Respiratory and Critical Care Medicine. 1994;**150**:1416-1422

[17] Aebli N, Krebs J, Davis G, Walton M, Williams MJ, Theis JC. Fat embolism and acute hypotension during

vertebroplasty: An experimental study in sheep. Spine [Phila Pa 1976]. 2002;**27**(5):460-466

[18] Wang AZ, Zhou M, Jiang W, Zhang WX. The differences between venous air embolism and fat embolism in routine intraoperative monitoring methods, transesophageal echocardiography, and fatal volume in pigs. The Journal of Trauma. 2008;**65**(2):416-423

[19] Kropfl A, Davies J, Berger U, Hertz H, Schlag G. Intramedullary pressure and bone marrow fat extravasation in reamed and unreamed femoral nailing. Journal of Orthopaedic Research. 1999;**17**(2):261-268

[20] Pape HC, Hildebrand F, Krettek C, Green J, Giannoudis PV. Experimental background—Review of animal studies. Injury. 2006;**37**(Suppl 4):S25-S38

[21] Matute-Bello G, Frevert CW, Martin TR. Animal models of acute lung injury. American Journal of Physiology. Lung Cellular and Molecular Physiology. 2008;**295**(3):L379-L399

[22] Takada M, Chiba S, Nagai T, Takeshita H, Kanno S, Ikawa T, et al. Inflammatory responses to neutral fat and fatty acids in multiple organs in a rat model of fat embolism syndrome. Forensic Science International. 2015;**254**:126-132

[23] Lim KR, Cho JM, Yoon CM, Lee KC, Lee SY, Ju MH. Correlation between the time elapsed after liposuction and the risk of fat embolism: An animal model. Archives of Plastic Surgery. 2018;**45**(1):14-22

[24] Mofid MM, Teitelbaum S, Suissa D, Ramirez-Montanana A, Astarita DC, Mendieta C, et al. Report on mortality from gluteal fat grafting: Recommendations from the ASERF Task Force. Aesthetic Surgery Journal. 2017;**37**(7):796-806

[25] Peltier LF, Wheller DH, BOYD HM, Scott JR. Fat embolism. II. The chemical composition of fat obtained from human long bones and subcutaneous tissue. Surgery. 1956;**40**(4):661-664

[26] Sherr S, Montemurno R, Raffer P. Lipids of recovered pulmonary fat emboli following trauma. The Journal of Trauma. 1974;**14**(3):242-246

[27] Peltier LF. Fat embolism following intramedullary nailing; report of a fatality. Surgery. 1952;**32**(4):719-722

[28] Peltier LF. Fat embolism: A pulmonary disease. Surgery. 1967;**62**(4):756-758

[29] Peltier LF. Fat embolism. A perspective. Clinical Orthopaedics and Related Research. 1988;**232**:263-270

[30] Wang AZ, Ma QX, Zhao HJ, Zhou QH, Jiang W, Sun JZ. A comparative study of the mortality rate of rats receiving a half lethal dose of fat intravenously: Under general anaesthesia versus under spinal anaesthesia. Injury. 2012;**43**(3):311-314

[31] Compton SK, Hamosh M, Hamosh P. Hydrolysis of triglycerides in the isolated perfused rat lung. Lipids. 1982;**17**:696-702

[32] Szabo G, Magyar Z, Reffy A. The role of free fatty acids in pulmonary fat embolism. Injury. 1977;**8**(4):278-283

[33] McIff TE, Poisner AM, Herndon B, Lankachandra K, Schutt S, Haileselassie B, et al. Fat embolism: Evolution of histopathological changes in the rat lung. Journal of Orthopaedic Research. 2010;**28**(2):191-197

[34] Poisner AM, Adler F, Uhal B, McIff TE, Schroeppel JP, Mehrer A, et al. Persistent and progressive pulmonary fibrotic changes in a model of fat embolism. Journal of Trauma and Acute Care Surgery. 2012;**72**(4):992-998

[35] Poisner AM, Herndon B, Lankachandra K, Likhitsup A, Al Hariri A, Kesh S, et al. Fat embolism sensitizes rats to a "second hit" with lipopolysaccharide: An animal model of pulmonary fibrosis. Journal of Trauma and Acute Care Surgery. 2015;**78**:552-557

[36] Poisner A, Herndon B, Bass D, Fletcher A, Jain A, England JP, et al. Evidence for angiotensin mediation of the late histopathological effects of fat embolism: Protection by losartan in a rat model. Experimental Lung Research. 2019;**44**:363-367

[37] Molteni A, Moulder JE, Cohen EF, Ward WF, Fish BL, Taylor JM, et al. Control of radiation-induced pneumopathy and lung fibrosis by angiotensin-converting enzyme inhibitors and an angiotensin II type 1 receptor blocker. International Journal of Radiation Biology. 2000;**76**(4):523-532

[38] Molteni A, Ward WF, Ts'ao CH, Solliday NH, Dunne M. Monocrotaline-induced pulmonary fibrosis in rats: Amelioration by captopril and penicillamine. Proceedings of the Society for Experimental Biology and Medicine. 1985;**180**(1):112-120

[39] Tan WSD, Liao W, Zhou S, Mei D, Wong WF. Targeting the renin-angiotensin system as novel therapeutic strategy x for pulmonary diseases. Current Opinion in Pharmacology. 2018;**40**:9-17

[40] McIff TE, Poisner AM, Herndon B, Lankachandra K, Molteni A, Adler F. Mitigating effects of captopril and losartan on lung histopathology in a rat model of fat embolism. The Journal of Trauma. 2011;**70**:1186-1191

[41] Fletcher A, Molteni A, Ponnapureddy R, Patel C, Pluym M, Poisner AM. The renin inhibitor aliskiren protects rat lungs from the histopathological effects of fat embolism. Journal of Trauma and Acute Care Surgery. 2017;**82**:338-344

[42] Marshall RP. The pulmonary renin-angiotensin system. Current Pharmaceutical Design. 2003;**9**(9):715-722

[43] Ahmed BA, Seda O, Lavoie JL. [Pro]renin receptor as a new drug target. Current Pharmaceutical Design. 2011;**17**(33):3611-3621

[44] Sealey JE, Rubattu S. Prorenin and renin as separate mediators of tissue and circulating systems. American Journal of Hypertension. 1989;**2**:358-366

[45] Sihn G, Rousselle A, Vilianovitch L, Burckle C, Bader M. Physiology of the [pro]renin receptor: Wnt of change? Kidney International. 2010;**78**(3):246-256

[46] Hennrikus M, Gonzalez AA, Prieto MC. The prorenin receptor in the cardiovascular system and beyond. American Journal of Physiology. Heart and Circulatory Physiology. 2018;**314**(2):H139-H145

[47] Silver RB, Reid AC, Mackins CJ, Askwith T, Schaefer U, Herzlinger D, et al. Mast cells: A unique source of renin. Proceedings of the National Academy of Sciences of the United States of America. 2004;**101**(37):13607-13612

[48] Dostal DE, Rothblum KN, Conrad KM, Cooper GR, Baker KM. Detection of angiotensin I and II in cultured rat cardiac myocytes and fibroblasts. The American Journal of Physiology. 1992;**263**:C851-C863

[49] Katwa LC, Campbell SE, Tyagi SC, Lee SJ, Cicila GT, Weber KT. Cultured myofibroblasts generate angiotensin peptides de novo. Journal of Molecular and Cellular Cardiology. 1997;**29**:1375-1386

[50] Iwai N, Matsunaga M, Kita T, Tei M, Kawai C. Regulation of renin-like enzyme in cultured human vascular smooth muscle cells. Japanese Circulation Journal. 1988;**52**:1338-1345

[51] Iwai N, Inagami T, Ohmichi N, Kinoshita M. Renin is expressed in rat macrophage/monocyte cells. Hypertension. 1996;**27**:399-403

[52] Gonzalez NC, Allen J, Schmidt EJ, Casillan AJ, Orth T, Wood JG. Role of the renin-angiotensin system in the systemic microvascular inflammation of alveolar hypoxia. American Journal of Physiology. Heart and Circulatory Physiology. 2007;**292**:H2285-H2294

[53] Veerappan A, O'Connor NJ, Brazin J, Reid AC, Jung A, McGee D, et al. Mast cells: A pivotal role in pulmonary fibrosis. DNA and Cell Biology. 2013;**32**(4):206-218

[54] Chao J, Blanco G, Wood JG, Gonzalez NC. Renin released from mast cells activated by circulating MCP-1 initiates the microvascular phase of the systemic inflammation of alveolar hypoxia. American Journal of Physiology. Heart and Circulatory Physiology. 2011;**301**(6):H2264-H2270

[55] Garbuzenko E, Berkman N, Puxeddu I, Kramer M, Nagler A, Levi-Schaffer F. Mast cells induce activation of human lung fibroblasts in vitro. Experimental Lung Research. 2004;**30**:705-721

[56] Poisner AM, Hamidpour S, Ho A, Skaria P, Fletcher A, Simon S, et al. Losartan blocks the recruitment of mast cells in the lungs of rats subjected to fat embolism with or without a second hit with LPS. The FASEB Journal. 2016;**30**:700.2

[57] Kesh S, Fletcher A, Voelker P, Guidos P, Poisner A, Tylski E, et al. Aliskiren, a direct renin inhibitor, reduces mast cell accumulation in lungs of rats after fat embolism. Q JM: An International Journal of Medicine. 2016;**109**(Suppl 1):S48

[58] Reilly CF, Tewksbury DA, Schechter NM, Travis J. Rapid conversion of angiotensin I to angiotensin II by neutrophil and mast cell proteinases. The Journal of Biological Chemistry. 1982;**257**:8619-8622

[59] Hultsch T, Ennis MF, Heidtmann HH. The role of chymase in ionophore-induced histamine release from human pulmonary mast cells. Advances in Experimental Medicine and Biology. 1988;**240**:133-136

[60] Tainsh KR, Pearce FL. Mast cell heterogeneity: Evidence that mast cells isolated from various connective tissue locations in the rat display markedly graded phenotypes. International Archives of Allergy and Immunology. 1992;**98**(1):26-34

[61] Irani AM, Schwartz LB. Mast cell heterogeneity. Clinical and Experimental Allergy. 1989;**19**(2):143-155

[62] Andersson CK, Mori M, Bjermer L, Lofdahl CG, Erjefalt JS. Novel site-specific mast cell subpopulations in the human lung. Thorax. 2009;**64**(4):297-305

[63] Poisner A, Herndon B, Al Hariri A, Qin C, Quinn T. Renin as a mediator of pulmonary damage caused by fat embolism and LPS. The FASEB Journal. 2013;**27**(1 Supplement):lb444

[64] Hamidpour S, Poisner A, Molteni A, Al-Husseinawi A, Colson J, Samir H, et al. Increased staining for renin/prorenin in the lungs in a rat model of fat embolism is enhanced by captopril and losartan which ameliorate the pulmonary damage. American Journal of Respiratory and Critical Care Medicine. 2018;**197**:A1859

[65] Das UN. Is angiotensin-II an endogenous pro-inflammatory

molecule? Medical Science Monitor. 2005;**11**(5):RA155-RA162

[66] Karnik SS, Unal H, Kemp JR, Tirupula KC, Eguchi S, Vanderheyden PM, et al. Angiotensin receptors: Interpreters of pathophysiological angiotensinergic stimuli. Pharmacological Reviews. 2015;**67**(4):754-819

[67] Gironacci MM. Angiotensin-[1-7]: Beyond its central effects on blood pressure. Therapeutic Advances in Cardiovascular Disease. 2015;**9**(4):209-216

[68] Klein N, Gembardt F, Supe S, Kaestle SM, Nickles H, Erfinanda L, et al. Angiotensin-[1-7] protects from experimental acute lung injury. Critical Care Medicine. 2013;**41**(11):e334-e343

[69] Uhal BD, Nguyen H, Dang M, Gopallawa I, Jiang J, Dang V, et al. Abrogation of ER stress-induced apoptosis of alveolar epithelial cells by angiotensin 1-7. American Journal of Physiology-Lung Cellular and Molecular Physiology. 2013;**305**(1):L33-L41

[70] Gonzalez NC, Wood JG. Alveolar hypoxia-induced systemic inflammation: What low PO[2] does and does not do. Advances in Experimental Medicine and Biology. 2010;**662**:27-32

[71] Dezso B, Nielsen AH, Poulsen K. Identification of renin in resident alveolar macrophages and monocytes: HPLC and immunohistochemical stu. Journal of Cell Science. 1988;**91**(Pt 1):155-159

[72] Chao J, Wood JG, Gonzalez NC. Alveolar hypoxia, alveolar macrophages, and systemic inflammation. Respiratory Research. 2009;**10**:54

[73] Zakheim RM, Mattioli L, Molteni A, Mullis KB, Bartley J. Prevention of pulmonary vascular changes of chronic alveolar hypoxia by inhibition of angiotensin I-converting enzyme in the rat. Laboratory Investigation. 1975;**33**(1):57-61

[74] Zakheim RM, Molteni A, Mattioli L, Park M. Plasma angiotensin II levels in hypoxic and hypovolemic stress in unanesthetized rabbits. Journal of Applied Physiology. 1976;**41**(4):462-465

[75] Mizuta K, Zhang Y, Mizuta F, Hoshijima H, Shiga T, Masaki E, et al. Novel identification of the free fatty acid receptor FFAR1 that promotes contraction in airway smooth muscle. American Journal of Physiology. Lung Cellular and Molecular Physiology. 2015;**309**(9):L970-L982

[76] Rohwedder A, Zhang Q, Rudge SA, Wakelam MJ. Lipid droplet formation in response to oleic acid in Huh-7 cells is mediated by the fatty acid receptor FFAR4. Journal of Cell Science. 2014;**127**(Pt 14):3104-3115

[77] Yukioka T, Yukioka N, Aulick LH, Goodwin CW, Mason AD Jr, Sugimoto T, et al. Evaluation of [1-sarcosine, 8-isoleucine] angiotensin II as a therapeutic agent for oleic acid-induced pulmonary edema. Surgery. 1986;**99**(2):235-244

[78] Lu G, Meier KE, Jaffa AA, Rosenzweig SA, Egan BM. Oleic acid and angiotensin II induce a synergistic mitogenic response in vascular smooth muscle cells. Hypertension. 1998;**31**(4):978-985

[79] Xiong L, Sun L, Liu S, Zhu X, Teng Z, Yan J. The protective roles of urinary trypsin inhibitor in brain injury following fat embolism syndrome in a rat model. Cell Transplantation. 2018;**963689718814766**:1-9

[80] Kiely DG, Cargill RI, Lipworth BJ. Acute hypoxic pulmonary vasoconstriction in man is attenuated by type I angiotensin II receptor

blockade. Cardiovascular Research. 1995;**30**:875-880

[81] Coonrod JD, Karathanasis P, Lin R. Lipoprotein lipase: A source of free fatty acids in bronchoalveolar lining fluid. Journal of Laboratory and Clinical Medicine. 1989;**113**(4):449-457

[82] Gal S, Bassett DJ, Hamosh M, Hamosh P. Triacylglycerol hyrolysis in the isolated, perfused rat lung. Biochimica et Biophysica Acta. 1982;**713**:222-229

[83] Okabe TF, Yorifuji HF, Murase TF, Takaku F. Pulmonary macrophage: A major source of lipoprotein lipase in the lung. Biochemical and Biophysical Research Communications. 1984;**125**:273-278

[84] Re RN, Cook JL. The mitochondrial component of intracrine action. American Journal of Physiology. Heart and Circulatory Physiology. 2010;**299**(3):H577-H583

[85] Hirabara SM, Silveira LR, Alberici LC, Leandro CV, Lambertucci RH, Polimeno GC, et al. Acute effect of fatty acids on metabolism and mitochondrial coupling in skeletal muscle. Biochimica et Biophysica Acta. 2006;**1757**(1):57-66

[86] Azekoshi Y, Yasu T, Watanabe S, Tagawa T, Abe S, Yamakawa K, et al. Free fatty acid causes leukocyte activation and resultant endothelial dysfunction through enhanced angiotensin II production in mononuclear and polymorphonuclear cells. Hypertension. 2010;**56**(1):136-142

[87] Shimokawa Y, Hirata K, Ishida T, Kojima Y, Inoue N, Quertermous T, et al. Increased expression of endothelial lipase in rat models of hypertension. Cardiovascular Research. 2005;**66**(3):594-600

[88] Watanabe S, Tagawa T, Yamakawa K, Shimabukuro M, Ueda S. Inhibition of the renin-angiotensin system prevents free fatty acid-induced acute endothelial dysfunction in humans. Arteriosclerosis, Thrombosis, and Vascular Biology. 2005;**25**(11):2376-2380

[89] Leeman M, Lejeune P, Naeije R. Inhibition of angiotensin-converting enzyme by perindopril diacid in canine oleic acid pulmonary edema. Critical Care Medicine. 1987;**15**(6):567-573

[90] Bruce E, Shenoy V, Rathinasabapathy A, Espejo A, Horowitz A, Oswalt A, et al. Selective activation of angiotensin AT2 receptors attenuates progression of pulmonary hypertension and inhibits cardiopulmonary fibrosis. British Journal of Pharmacology. 2015;**172**(9):2219-2231

[91] Chuang EL, Miller FS, Kalina RE. Retinal lesions following long bone fractures. Ophthalmology. 1985;**92**(3):370-374

[92] Lee JE, Jea SY, Oum BS, Kim HJ, Ohn YH. Effect of fat embolism with triolein emulsion on blood-retinal barrier. Ophthalmic Research. 2009;**41**(1):14-20

[93] Choudhary R, Kapoor MS, Singh A, Bodakhe SH. Therapeutic targets of renin-angiotensin system in ocular disorders. Journal of Current Ophthalmology. 2017;**29**(1):7-16

[94] Berlot G, Bussani R, Shafiei V, Zarrillo N. Fulminant cerebral fat embolism: Case description and review of the literature. Case Reports in Critical Care. 2018;**7813175**

[95] Jackson L, Eldahshan W, Fagan SC, Ergul A. Within the brain: The renin angiotensin system. International Journal of Molecular Sciences. 2018;**19**(3):876-879

Chapter 3

Non-Malignant Cardiac Tumors

Sarah Eapen, Bethany Malone, Jennifer Hanna and Michael S. Firstenberg

Abstract

Cardiac tumors represent an unusual clinical problem in that they are often discovered as an incidental finding during a routine echocardiogram or in the course of a work-up for a source of embolism. Malignant tumors of the heart are either defined as primary or metastatic from an extra-cardiac primary source—regardless, the prognosis is poor. However, there are several cardiac tumors that are characterized as being non-malignant with regard to their tumor biology, but their tendencies to cause embolic or obstructive complications can be just as catastrophic despite a lack of invasiveness or potential to metastasize. The purpose of this chapter is to review the common types of non-malignant cardiac tumors with regard to their incidence, presentation, potential for complications, and management—with emphasis on surgical indications and techniques.

Keywords: cardiac tumor, myxoma, fibroelastoma, cardiac surgery, benign tumors, cardiac lipomas, heart disease

1. Introduction

Embolic strokes are one of the most devastating medical conditions with regard to the overall impact on quality and quantity of life. Once an embolic complication occurs, management options are sometimes limited, but a critical aspect of appropriate disease management is searching for a source of embolism. The same concepts hold true with peripheral embolisms. Part of the rationale for the search for a source is to help determine optimal therapies with the goal of reducing addition embolic events and further complications. Despite substantial resources devoted to stroke (and embolic) prevention, it still remains a considerable problem.

A recent report by the American Heart Association illustrates the enormous burden that strokes represent to society. A cerebrovascular event (i.e., a stroke) occurs every 40 seconds in the United States with a related death occurring every 3.7 minutes [1]. While the causes of strokes are complex and often multi-factorial, cardiac sources represent a common etiology. Atrial fibrillation and associated left atrial appendage thrombi are one of the more frequently encountered sources [2]. Even though mechanical left atrial appendage closure or systemic anticoagulation remain the standard of care for treatment [3], it is important to consider that there are a variety of other cardiac-related causes of embolism and stroke. The most common non-thrombotic causes of cardiac embolism are infectious and non-infectious endocarditis—a topic that is the focus of other chapters [4].

The focus of this chapter is non-malignant and non-infectious cardiac masses—with an emphasis on diagnosis and management. Cardiac tumors are often

delineated as malignant and non-malignant with malignant tumors being either primary (i.e., cardiac sarcomas) or metastatic (i.e., breast carcinoma). They are distinguished from non-malignant tumors, such as myxomas and fibroelastomas, in that the latter, despite the pathologic implications of growth (i.e., valvular obstruction) and systemic embolism, lack true metastatic potential. Nevertheless, non-malignant cardiac tumors can be clinically devastating (i.e., malignant) by their tendency to cause potentially devastating, and occasionally fatal, embolic complications [5].

2. Methods

The focus of this review is on non-malignant tumors. The review methods consisted of Google Scholar (https://scholar.google.com) and PubMed (https://www.ncbi.nlm.nih.gov/pmc/) searches with emphasis on the following key words: cardiac tumors, benign cardiac masses, myxomas, fibroelastomas, and fibromas. Additional associated search terms included: surgery, diagnosis, imaging, and management. Selected references, including manuscript abstracts and full texts, were reviewed for relevance in the context of this review.

3. Myxomas

Cardiac tumors are rare, occurring at a frequency of 0.0017–0.33% [6]. Cardiac myxomas are one of the most common, comprising 77% of surgically excised tumors in autopsy series [7]. Myxomas affect females predominantly with an incidence 1.5–2 times that of males [8]. The average age at presentation is 53 [8]. The majority of myxomas are sporadic. Inherited forms are less common, seen in 7% of myxomas [9]. Initially reported by Carney in 1985, cardiac myxomas seen in association with pigmented skin lesions and endocrine tumors are collectively known as Carney complex, an autosomal dominant genetic disorder. Familial myxomas tend to affect younger patients and have a higher prevalence among females. In addition, they are more often multicentric with higher rates of embolism and recurrence following resection [9].

Myxomas tend to be rare tumors of mesenchymal origin. They are comprised of stromal cells and are characterized as being benign (**Figure 1**). Biochemically, they

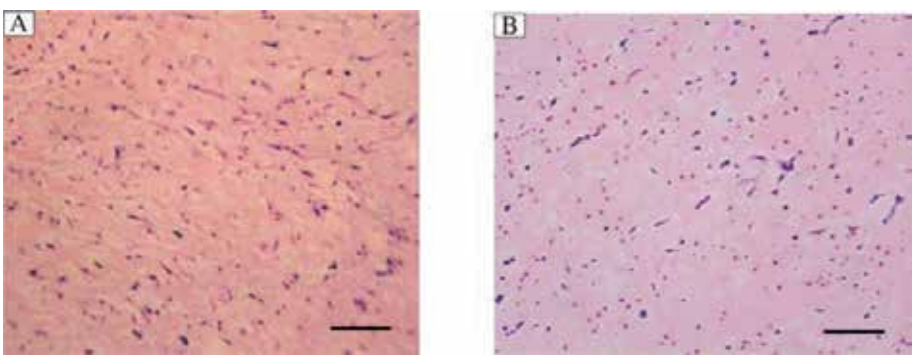

Figure 1.
Histology of cardiac myxoma. Representative histology of cardiac myxoma tissue in a 26-year-old woman with multiple recurrences of cardiac myxoma (HE, 100×). A: Tumor in 2005. B: Tumor in 2010. Similar histologic appearance of A and B with irregular and papillary proliferations in the myxoid stroma. Bar = 30 μm [10].

have been correlated with increased production of interleukin 6 (IL-6), however, the significance of this is unclear [11]. While ocular, cutaneous, intramuscular, and juxta-articular involvement has been described, the most common presentation is intra-cardiac with most (85%) involving the left atrium [12].

Cardiac myxomas are typically solitary lesions and most commonly arise from the septal endocardium near the fossa ovalis [8]. 85% arise from the left atrial septum and 11% arise from the right atrial septum [7]. The clinical presentation of myxomas is dependent on tumor location. When confined to the left atrium, myxomas present with symptoms of mitral valve stenosis [13]. Dyspnea and orthopnea result from pulmonary edema and left-sided heart failure. Conversely, right atrial myxomas cause tricuspid valve stenosis, leading to symptoms of right-sided heart failure [13]. In 22% of patients, embolism may occur, leading to symptoms of peripheral ischemia or stroke [8]. 20% of patients develop systemic symptoms, which are attributed to production of IL-6 by tumor cells [14]. Rarely, myxomas may become infected with symptoms similar to those of infective endocarditis [13].

Echocardiography is the primary diagnostic modality for cardiac myxomas [15]. Typical echocardiographic findings are of a mobile mass arising from the septal endocardium, attached by a narrow stalk. Echocardiography is preferred to MRI and CT imaging due to enhanced spatial and temporal resolution. If echocardiography is non-diagnostic, MRI findings of a heterogeneous mass bright on T2-weighted imaging and CT findings of a heterogeneous mass with low attenuation are consistent with myxoma (**Figures 2** and **3**) [15]. Advanced imaging is often performed to help differentiate "benign" myxomas from more aggressive or potentially malignant cardiac tumors that might require a more comprehensive oncologic management strategy (i.e., aggressive debulking, adjuvant chemotherapy, or even palliative care for advanced tumors). While the imaging characteristics, as described above, of myxomas are often diagnostic, unusual appearing masses might prompt further imaging to rule-out other tissue types. The differential diagnosis for such masses includes teratomas (rare), lipomas, angiosarcomas, rhabdomyomas, and rhabdomyosarcomas [18]. Distinguishing characteristics often consist of intramyocardial tumor invasion on imaging. Tissue biopsy is rarely indicated as the risk of embolism from endomyocardial biopsies will typically prompt definitive surgical resection for primary diagnosis and therapeutic intervention. Tumor location and imaging characteristics, along with a detailed history and physical, can also help distinguish cardiac tumors from other types of intra-cardiac pathology, such as endocarditis or thrombus. A recent history of acute myocardial infarction or known left ventricular

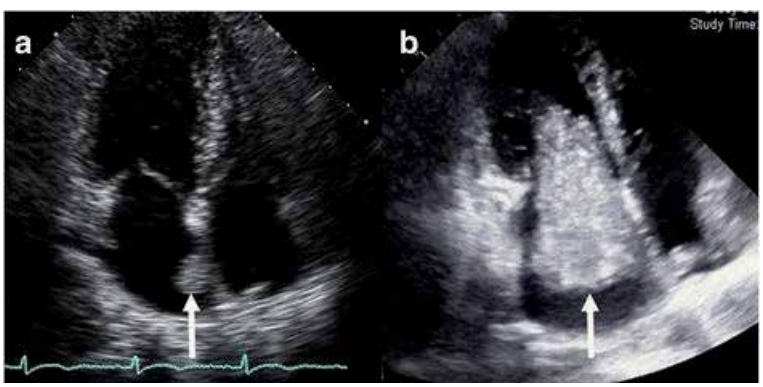

Figure 2.
Representative echocardiographic images of a large left atrial myxoma. From: Surgical resection of cardiac myxoma. Images of a rapidly growing myxoma. (a): A small myxoma is attached to the left atrial side of the fossa ovalis. (b): An enlarged myxoma passes in and out of the mitral valve according to the cardiac cycle [16].

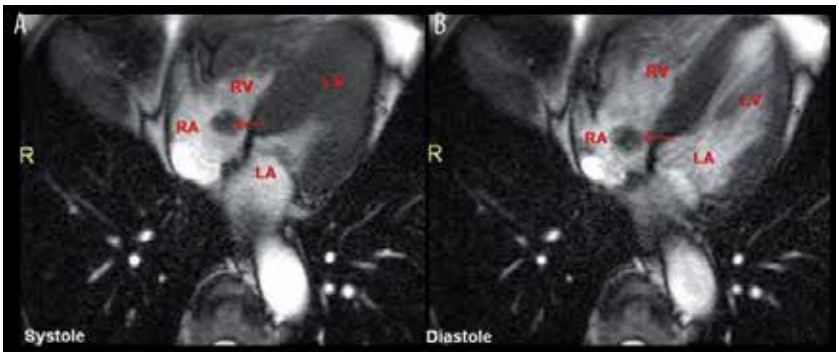

Figure 3.
Representative cardiac MRI demonstrating a right atrial myxoma. Right atrial myxoma causing syncope. A: Cardiac MRI showing atrial myxoma during systole. B: Cardiac MRI showing atrial myxoma during diastole. RA, Right atrium; RV, Right ventricle; LA, Left atrium; LV, Left ventricle; arrow—Myxoma [17].

dysfunction might predispose to apical thrombus just as a history of atrial fibrillation is known to predispose to left atrial or left atrial appendage thrombus [19, 20].

Histologically, myxomas are composed of stellate mesenchymal cells in a background of myxoid stroma. Myxoma cells are variably positive for S-100, CD31, and CD34 [13]. In addition, 73.9% of cardiac myxomas express calretinin [21]. Inactivating mutations in the PRKAR1A gene are observed in both sporadic and non-sporadic myxomas. For this reason, routine immunohistochemical staining for PRKAR1A is recommended [22].

Recommended treatment for suspected cardiac myxomas, regardless of size, is immediate surgical resection due to embolic risk [23]. Tumor size ≥ 4.5 cm and soft tumors have been identified as independent risk factors for embolism. Prognosis is favorable with a 92.7% 10-year survival rate following surgical resection. Tumor recurrence is extremely rare. Multicentricity, observed with Carney complex, is an independent risk factor for recurrence following surgical resection [23]. Recurrence has been associated with incomplete resection and family history of complex or multiple myxomas [24]. In general, recurrence rates are typically less than 3%, often in complex or unusual cases [25].

4. Papillary fibroelastomas

Papillary fibroelastomas comprise less than 10% of primary cardiac tumors and are the most common primary tumor of cardiac valves (**Figure 4**) [14]. Men and women are affected equally at an average age of 60. Fibroelastomas are now thought to be more prevalent than myxomas, contradicting previous autopsy series in which myxomas were the most common primary intracardiac tumor [26]. Their etiology is unclear with development related to organizing thrombi, hamartoma proliferation, chronic viral endocarditis, and repeated hemodynamic trauma [27]. Iatrogenic cases of fibroelastomas following thoracic radiation and cardiac surgery have also been described, though these are typically non-valvular [28]. Fibroelastomas are valvular in 90% of cases, most commonly involving the aortic and mitral valves [29]. Less commonly, the left ventricular endocardium and tricuspid valves are affected [15]. Diseased valves are affected in 69.5% of cases, specifically post-rheumatic valves in 37.8% and fibrotic calcified valves in 62.2%. This finding has led some to speculate that a contributing factor to their development is repeated trauma to the cardiac valve surface from abnormal intra-cardiac blood flow and turbulence [13].

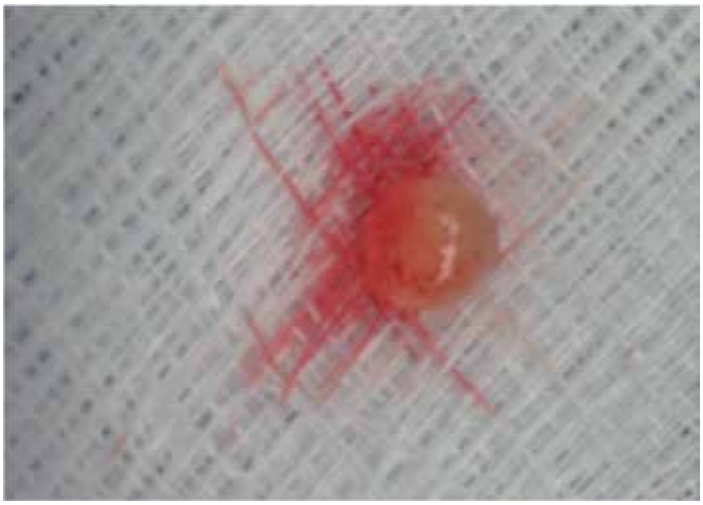

Figure 4.
Surgical specimen of a fibroelastoma. Surgical specimen of an incidental 5 mm fibroelastoma found during routine intra-operative transesophageal echocardiography in a patient undergoing routine coronary artery bypass surgery.

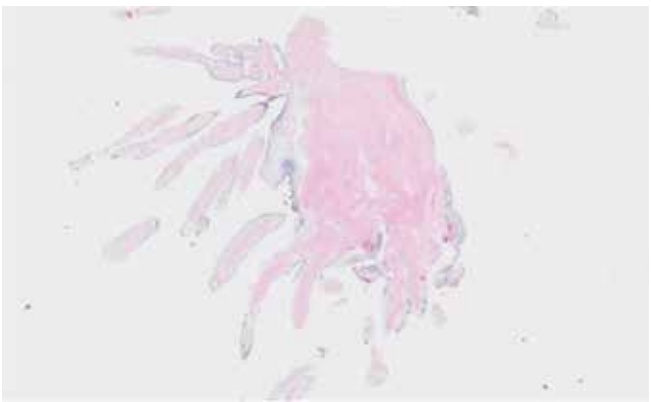

Figure 5.
Photomicrograph of a fibroelastoma. Photomicrograph of papillary fibroelastoma. From: Robotic excision of aortic valve papillary fibroelastoma and concomitant maze procedure [30].

Clinically, fibroelastomas may present with acute embolism following platelet and fibrin aggregation [8]. Alternatively, prolapse of fibroelastomas adjacent to coronary ostia may lead to angina, syncope, and sudden death. The diagnosis is made by echocardiography, which demonstrates a small, homogenous mobile mass attached to a valve by a short pedicle [15]. They have characteristic papillary fronds and resemble sea anemones (**Figure 5**) [31]. These papillary projections give fibroelastomas characteristic stippled edges on echocardiographic imaging [32]. Fibroelastomas may be mistaken for Lambl's excrescences, which are mobile frond-like lesions that occur along lines of valve closure [33]. Interestingly, there have been some anecdotal reports of spontaneous regression. For this reason, intraoperative transesophageal echocardiography is clearly indicated prior to surgical intervention [34]. However, these reports should not be used to advocate non-operative management except in very high-risk patients. In addition, there is no evidence to suggest a role for anti-platelet or anti-coagulation therapy as a means of treatment or secondary prevention once an embolic complication occurs. Nevertheless, in

patients who are not surgical candidates, such medical therapy might be reasonable. In theory, very small tumors could be drawn into the cardiopulmonary bypass circuit or surgical suction prior to excision precluding pathologic evaluation. In such cases, pre- and post-bypass imaging is critical to not only confirm the diagnosis, but also to demonstrate resection.

Although transthoracic echocardiography can be used to screen for papillary fibroelastomas, transesophageal echocardiography is preferred due to higher resolution and enhanced imaging capability (**Figure 6**) [36]. Multiplanar transesophageal echocardiography identifies the exact point of endocardial attachment, which facilitates operative planning. One of the limitations of echocardiography is its inability to stratify risk of embolization based on lesion characteristics [37]. Fibroelastomas are usually not visualized on MRI and CT imaging [15]. Histologically, fibroelastomas have a central core of dense connective tissue, which is surrounded by loose connective tissue and lined with hyperplastic endothelial cells [31]. These surface endothelial cells express vimentin and CD34. These findings have unclear clinical significance, but are helpful in establishing a pathologic diagnosis [13].

Surgical resection sparing underlying valve tissue is recommended in cases of papillary fibroelastoma. In a study of 511 cases over a 15-year period at the Mayo Clinic, 185 patients (36.2%) underwent surgical resection [37]. Primary excision was performed in 51% while excision as an adjunct to other cardiac surgery was performed in 49%. The aortic valve was most commonly affected and in 98% of cases, the native valve was preserved. Three hundred and twenty-six patients (63.8%) with echocardiographic findings of papillary fibroelastoma were managed non-operatively. Patients with papillary fibroelastoma suspected on echocardiography who did not undergo surgical resection had higher rates of stroke and mortality [37].

In the above described Mayo Clinic operative series, there was a 98% native valve preservation rate and 1.6% recurrence rate. Most importantly were their neurologic embolic outcomes. For the surgical population, the stroke risk was 2% at 1 year and 8% at 5 years. This rate was approximately 2.5x age-matched controlled. For the medically managed patients, the 1- and 5-year stroke risk was significantly higher than the operative group at 6 and 13%, respectively. There were 29 observed strokes versus 8.4 expected. Obviously, it was difficult to determine the impact of confounding risk factors that might have increased the stroke risk in patients who were otherwise poor surgical candidates. Regardless, the incidence was still nearly 3.5× that of matched controls. Furthermore, in the non-operative group, medical management with anti-thrombotic therapy (i.e., anti-platelet and anti-coagulant therapy, including dual therapy) had no impact on the stroke risk at 5 years when compared

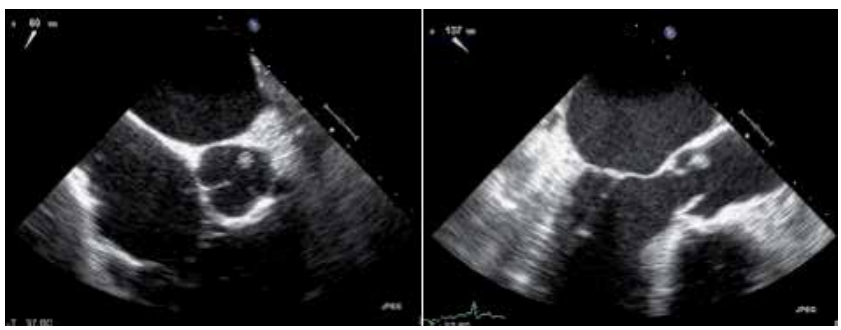

Figure 6.
Echocardiographic imaging of a fibroelastoma. Fibroelastoma of the aortic valve. Short and long axis view transesophageal echocardiography. From: Surgery for cardiac papillary fibroelastoma: A 12-year single institution experience [35].

to those without anti-thrombotic therapy [37]. Overall, the authors did not find any echocardiographic or clinical variables that helped stratify patients into high- or low-risk groups for embolic complications. The significant increased stroke risk in the non-operative group (even when matched for age-adjusted controls) and the lack of benefit of medical therapies serve as contemporary evidence to justify surgical management as first-line therapy in appropriate risk-stratified patients (**Figure 7**).

Surgical intervention for papillary fibroelastoma should be considered in patients who are symptomatic, undergoing cardiac surgery for other reasons, or have large, highly mobile lesions [38]. Further study through randomized controlled, multicenter trials is needed to determine if the potential benefit of surgical resection outweighs risk in asymptomatic patients. In asymptomatic patients who are otherwise good surgical candidates, the decision for non-operative management should be well-documented as part of shared decision-making with the patients with emphasis on the theoretical risks and benefits of surgery versus the risks of embolic complications.

In another single-center review, there was a tendency for occurrence in elderly males (71% males and 57% older than 61 years of age). Most (72%) occurred on a cardiac valve. Rarely was more than 1 lesion encountered and rarely were they >1.5 cm in size (27.8%). Surgical management was uncomplicated in all cases, even though some patients required concomitant surgery (i.e., coronary artery bypass grafting), and 30-day survival was 100%. No recurrences were reported at 1-year follow-up [39]. Similar outcomes were reported from another large-volume program in which Mkalaluh and colleagues reported 0 peri-operative mortalities in 11 patients (7 of whom had valvular involvement) with 100% 1-year survival and 91% survival at a mean follow-up of 4.2 years [40].

The indications for surgical resection are often a function of presentation and whether the patient is an appropriate surgical candidate. Since many fibroelastomas are incidental findings and hence asymptomatic, the natural history is unclear even though their tendency to embolize as pedunculated masses is unpredictable. For this reason, in appropriate surgical candidates, the presence of a presumed fibroelastoma is often an indication for surgical management, especially with left-sided

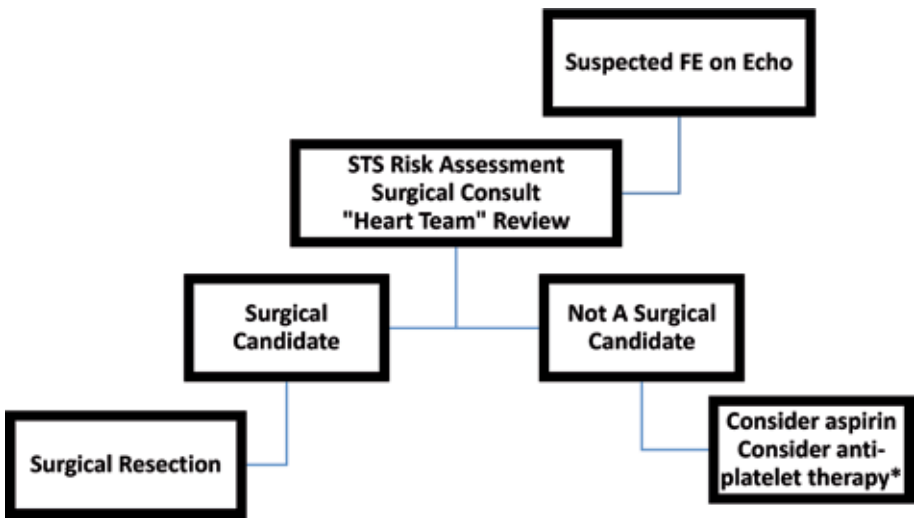

Figure 7.
Proposed algorithm for left-sided possible fibroelastoma. Legend: Adopted from Tamin et al. [37]. FE: Fibroelastoma. Note: there is little evidence to support the overall recommendation for anti-platelet or anti-coagulant therapy in this population.

lesions. While tumor size has not been correlated with embolic risk [41], there is some evidence to suggest that in medically managed patients, the risk of neurologic events was as high as 22% [42]. Nevertheless, the risks of non-operative management are poorly understood. Advocating for surgical intervention must be individualized as part of shared decision-making [43].

5. Cardiac lipomas

Cardiac lipomas, much like lipomas encountered elsewhere in the body, are typically composed of mature adipose (fat) cells and are well-encapsulated. The majority of cardiac lipomas are subendocardial (50%), while the remainder are myocardial (25%) or subpericardial (25%) (**Figure 8**). They are typically found in the left ventricle or right atrium. Embolic complications are extremely rare unless the tumor is coated with thrombus from abnormal flow patterns. Typically, the presentation is characterized by obstructive symptoms [46, 47]. Surgical resection is typically reserved for symptomatic patients and consistent of removal of the entire capsule with pericardial reconstruction of the residual defect if necessary [48]. Asymptomatic patients can be managed expectantly. It is important to note that lipomas must be distinguished from lipomatous hypertrophy of the intra-atrial septum. Lipomatous hypertrophy is considered a benign infiltrative process of the adipose septal tissue. However, obstructive symptoms and even complex atrial arrhythmias can develop from cellular proliferation. In such symptomatic cases, surgical debulking and reconstruction may be considered [49].

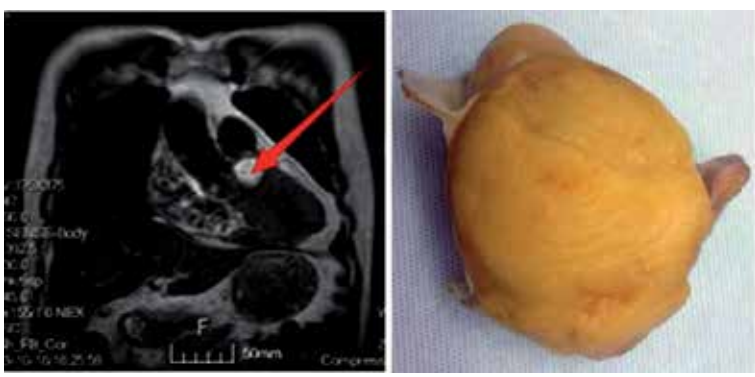

Figure 8.
MRI and surgical specimen of a cardiac lipoma. Left figure: Cardiac lipoma in the interventricular septum. Cardiac MRI showed a round-like signal, measuring 36 × 20 mm, in the upper portion of IVS, anterior to the right coronary sinus of aorta [44]. Right figure: Cardiac lipoma. The surface of the specimen is lined by smooth endocardial and epicardial tissue. The cut surface displays a yellow, lobulated appearance without hemorrhage, necrosis, fleshy change, or calcification [45]. Note: The surgical specimen is from the same patient as the MRI (both cc: Figures with this marker are used under the terms of Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms).*

6. Unusual/rare non-malignant cardiac tumors

While myxomas and fibroelastomas are the most common forms of non-malignant cardiac tumors, other cellular types have been encountered as intra-cardiac masses. Most are considered extremely rare and limited to cases

reports or small series from large institutions. These masses include teratomas, hamartomas, fibromas, hemangiomas, paragangliomas, and mesotheliomas of the atrioventricular node [50, 51]. Management is often similar to other cardiac masses and based on presenting symptoms, concern for embolic risk or obstructive physiology, and clinical risk of surgical intervention [52]. Because of the rarity of these types of tumors, little is known about pre-operative incidence. A definitive tissue diagnosis is often made at the time of surgical resection [53]. Unlike myxomas and fibroelastomas, embolic complications of these unusual tumors are rare. Patients typically present with obstructive heart failure symptoms. As most are asymptomatic, they are often only encountered at autopsy and are rarely considered the cause of death [54]. Resection or debulking is typically indicated based on presentation, tumor location (especially with regard to surrounding cardiac structures), and size. However, some patients with large tumors, presumed to be benign or potentially curative with resection, might need cardiac transplantation if safe resection is not possible [55]. Most ventricular fibromas can undergo safe resection, even if the tumor involvement is extensive, with good short- and long-term results and trivial risk of recurrence [56]. In general, symptoms of heart failure and arrhythmias resolve with resection. Asymptomatic tumors that fit into this category can be managed expectantly with serial imaging.

7. Surgical management of benign cardiac tumors

The surgical management of non-malignant cardiac tumors varies depending on the location of the tumor and the potential involvement of intra-cardiac structures [57]. Not only is the oncologic principle of wide excisional margins is not always possible due to the critical nature of certain cardiac structures, it is not necessary. The key principle is complex tumor excision if possible. Unless the diagnosis is obvious based on presentation, location, and clinical appearance, non-malignant tumors can often be confused with subacute endocarditis or intra-cardiac thrombus. Nevertheless, complex excision is necessary. Fibroelastomas can often be the easiest to remove, typically by sharp excision from their adherent structures. Even with valvular involvement, it would be uncommon to require leaflet reconstruction or valve replacement.

Intra-cardiac excisions, almost by definition, require cardiopulmonary bypass, aortic cross-clamping, and cardiac arrest. The specific techniques are beyond the scope of this chapter, as are the advantages and disadvantages of choice of incision (i.e., conventional full sternotomy, minimally-invasive sternal or right thoracotomy, or robotic-assisted techniques) and myocardial protection. The approach is probably best left to the individual comfort level and skill of the surgeon [58]. Nevertheless, because focused resection compared to wide debridement is typically the surgical goal, minimally-invasive approaches may be reasonable in appropriately selected patients. Cannulation techniques will vary depending on the tumor location. However, there should be a low threshold for bi-caval cannulation to assist in access to the atrial chambers and possible resection and reconstruction of the intra-atrial septum. In addition, root venting should always be considered, even with primary right-sided structures, as communication or left-sided involvement might introduce intra-cardiac air that would require appropriate de-airing upon weaning from cardiopulmonary bypass.
In patients with concomitant cardiovascular pathology (i.e., coronary artery disease, aortic aneurysms, or separate valvular pathology), appropriate surgical intervention should be performed. The decision to perform a preoperative cardiac

catheterization should be based on an appropriate multi-disciplinary assessment of the risks of underlying coronary artery disease, risks of the procedures (i.e., catheter-induced dislodgement of the tumor), and the age and co-morbidities of the patient as suggested by clinical guidelines [59]. In situations in which cardiac catheterization is either relatively contraindicated (i.e., presence of an aortic valve mass) or perceived to be of low clinical benefit, coronary computed tomography might be considered and potentially helpful in guiding therapy [60]. Intra-operative transesophageal echocardiography should be used routinely to ensure an accurate diagnosis, clear identification of involved structures, and complete resection prior to surgical closure [61].

For tumors that involve either the aortic valve or left ventricular outflow track, the surgical approach should be trans-aortic—essentially a similar approach as is used for traditional aortic valve replacement surgery. Aortic valve replacement is rarely necessary. Careful trans-aortic exposure to the left ventricular outflow track can provide access to tumors in the LVOT or on the left ventricular side of the anterior leaflet of the mitral valve. Even residual aortic or mitral insufficiency, either primary insufficiency or as a consequence of resection, can be well tolerated for many years. The indications for valve replacement in such cases should be limited to those patients in whom residual regurgitation would otherwise require repair or replacement based upon current guidelines for valvular dysfunction management [62].

For tumors that involve an isolated valve, a standard surgical approach to the specific valve is typically employed based on surgeon preference, i.e., trans-right atrial for tricuspid pathology and right ventricular masses. For masses such as myxomas that involve the intra-atrial septum, a variety of approaches can be used. The most common approach is through the right atrium (even if the tumor is on the left atrial side of the septum) with excision of the fossa ovalis or the involved intra-atrial septum to remove not only the tumor, but the stalk and the potential "tumor roots" in the septal tissue (**Figure 9**). Even with large tumors, primary reconstruction of the intra-atrial septum can be often performed as the size (width and length) of the associated stalk rarely correlates with the actual extent of septal tissue involvement. For large septal defects, reconstruction with bovine pericardium can easily be performed [16]. Depending on surgeon experience, preference, and tumor location, a right thoracotomy approach to either the left or right atrium can be considered [63]. While a left atrial approach has been described for tumors on the left atrial side of the intra-atrial septum, if such an approach is chosen, it is critical that the principles of complex tumor excision, including the stalk and septal roots (with reconstruction of the intra-atrial septum if necessary), be maintained [64]. Merely shaving the tumor off the intra-atrial septum without resecting the septal tissue is inappropriate as it might leave residual tumor behind and predispose to tumor recurrence.

All surgical excisions should be sent for pathology and microbiology. A comprehensive pathological evaluation is critical as many tumors have extensive thrombotic material covering them that might confound a true diagnosis. Occasionally, tumors can become infected with presentations similar to endocarditis. When encountered, a prolonged course of targeted antibiotic therapy is recommended, as with any form of endocarditis. Likewise, microbiologic assessment of the mass is necessary to rule out a potentially infectious etiology, especially in the absence of a clear preoperative diagnosis. Concomitant infected tumors, while part of any differential diagnosis, are rare [65].

Post-operative management should be consistent with that of any other post-cardiotomy patient. Anti-coagulation should only be considered if indicated for other reasons, such as if recommended by neurologic consultants for the

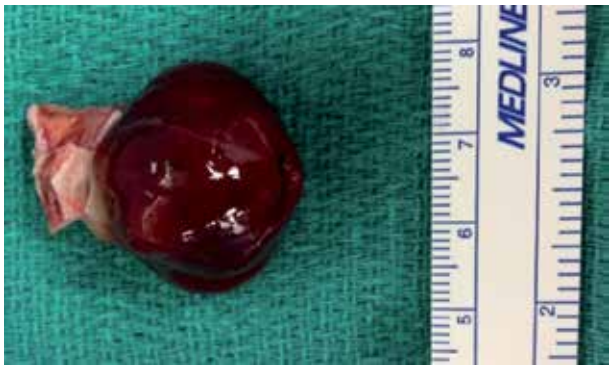

Figure 9.
Surgical specimen of a left atrial myxoma. Approximately 3 cm left atrial cardiac myxoma surgical specimen. Note the resected intra-atrial septal tissue.

treatment of embolic strokes. For patients whose tumors appear to have a large thrombus burden, a hypercoagulable state work-up and appropriate treatment should be considered. Guidelines for post-resection imaging surveillance are lacking and should be symptom-based unless there is concern for incomplete resection or recurrence.

8. Summary

Intra-cardiac masses represent a challenging clinical problem. Patients often present with embolic complications or obstructive heart failure symptoms. Alternatively, they may be asymptomatic with the mass discovered as an incidental finding in work-up of an alternative diagnosis or in preparation for other therapies (i.e., coronary artery bypass surgery). As discussed, such tumors are rare and must be distinguished from other cardiac masses, specifically endocarditis and intra-cardiac thrombus for which the management strategies are well-established. The overriding principle of management is prevention of potentially catastrophic embolic complications, specifically neurologic events. However, the data to support this approach is either limited or not based on high-quality randomized or controlled trials [3, 29]. As such, when encountered in appropriately risk-stratified patients, surgical removal is often curative and should be considered first-line therapy. While STS risk scoring is often used to evaluate these patients, a specific risk-model for treatment is not part of the STS calculator. However, it most closely matches the risks for patients undergoing valve repair or replacement (http://riskcalc.sts.org/stswebriskcalc/calculate), Risk for recurrence is low and post-operative survival is excellent. While medical management of these masses is considered in high-risk patients and those who refuse surgery, it is important to consider there is little data to support this approach and some evidence to suggest an increased stroke risk. Medical management, specifically anti-thrombotic therapies, have little role and can potentially delay a diagnosis until a catastrophic neurologic event occurs. It should only be considered in unusual cases. Furthermore, while the mere presence of an intra-cardiac mass is considered an indication for surgical resection, if there are concerns about the diagnosis based on echocardiographic characteristics or if there is concern for an invasive primary or metastatic malignant tumor, CT or MRI imaging can be useful. Given the rarity of these tumors, if there are any concerns about the diagnosis or management, referral to a tertiary care center should be considered.

9. Conclusions

Intra-cardiac masses are rare, but are occasionally found during work-up for a source of embolism or encountered as an incidental finding. Tumor location and echocardiographic characteristics often suggest a diagnosis. However, definitive surgical resection for both diagnostic and therapeutic reasons should be considered first-line therapy. Patients managed non-operatively have increased risk for embolic complications. Medical therapies have not been shown to be effective although definitive data is lacking and controlled trials may be difficult to perform.

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References

[1] Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics—2018 update: A report from the American Heart Association. Circulation 2018;137(12):e67-492

[2] Khurram IM, Dewire J, Mager M, Maqbool F, Zimmerman SL, Zipunnikov V, et al. Relationship between left atrial appendage morphology and stroke in patients with atrial fibrillation. Heart Rhythm. 2013;**10**(12):1843-1849

[3] Holmes DR, Doshi SK, Kar S, Price MJ, Sanchez JM, Sievert H, et al. Left atrial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation: A patient-level meta-analysis. Journal of the American College of Cardiology. 2015;**65**(24):2614-2623

[4] Firstenberg MS. Introductory chapter: Introduction to advanced concepts in endocarditis. In: Firstenberg MS, editor. Advanced Concepts in Endocarditis. London: IntechOpen; 2018. p. 79883. DOI: 10.5772/intechopen. Available from: https://www.intechopen.com/books/advanced-concepts-in-endocarditis/introductory-chapter-introduction-to-advanced-concepts-in-endocarditis

[5] Butany J, Nair V, Naseemuddin A, Nair GM, Catton C, Yau T. Cardiac tumours: Diagnosis and management. The Lancet Oncology. 2005;**6**(4):219-228

[6] Wold LE, Lie JT. Cardiac myxomas: A clinicopathologic profile. The American Journal of Pathology. 1980;**101**:219-240

[7] Burke AP, Virmani R. Tumors of the Heart and Great Vessels. Atlas of Tumor Pathology. Washington, DC: Armed Forces Institute of Pathology; 1996. pp. 1-11

[8] Burke A, Tavora F. The 2015 WHO classification of tumors of the heart and pericardium. Journal of Thoracic Oncology. 2016;**11**(4):441-452

[9] Wei K, Guo HW, Fan SY, Sun XG, Hu SS. Clinical features and surgical results of cardiac myxoma in carney complex. Journal of Cardiac Surgery. 2019;**34**:14-19

[10] Cao H et al. Journal of Biomedical Research. 2011;**25**(5):368-372

[11] Seino Y, Ikeda U, Shimada K. Increased expression of interleukin 6 mRNA in cardiac myxomas. British Heart Journal. 1993;**69**(6):565-567. DOI: 10.1136/hrt.69.6.565. PMC 1025174. PMID 8343326

[12] Knepper LE, Biller J, Adams HP, Bruno A. Neurologic manifestations of atrial myxoma. A 12-year experience and review. Stroke. 1988;**19**(11):1435-1440. DOI: 10.1161/01.str.19.11.1435. PMID 3188128

[13] Burke AP, Tazellar H, Gomez-Roman J, et al. WHO Classification of Tumours. Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart. Lyon: IARC Press; 2004. pp. 260-265

[14] Wang JG, Li YJ, Liu H, et al. Clinicopathologic analysis of cardiac myxomas: Seven years' experience with 61 patients. Journal of Thoracic Disease. 2012;**4**(3):272-283

[15] Araoz PA, Mulvagh SL, Tazelaar HD, Julsrud PR, Breen JF. CT and MR imaging of benign primary cardiac neoplasms with echocardiographic correlation. Radiographics. 2000;**20**(5):1303-1319

[16] Lee KS, Kim GS, Jung Y, Jeong IS, Na KJ, Oh BS, et al. Surgical resection of cardiac myxoma—A 30-year single institutional experience. Journal of Cardiothoracic Surgery. 2017;**12**(1):18

[17] Animashaun IB, Akinseye OA, Akinseye LI, Akinboboye OO. Right atrial myxoma and syncope. The American Journal of Case Reports. 2015;**16**:645-647

[18] Kassi M, Polsani V, Schutt RC, Wong S, Nabi F, Reardon MJ, et al. Differentiating benign from malignant cardiac tumors with cardiac magnetic resonance imaging. The Journal of Thoracic and Cardiovascular Surgery. 2019;**157**(5):1912-1922

[19] McCarthy CP, Vaduganathan M, McCarthy KJ, Januzzi JL, Bhatt DL, McEvoy JW. Left ventricular thrombus after acute myocardial infarction: Screening, prevention, and treatment. JAMA Cardiology. 2018;**3**(7):642-649

[20] Di Minno MN, Ambrosino P, Russo AD, Casella M, Tremoli E, Tondo C. Prevalence of left atrial thrombus in patients with non-valvular atrial fibrillation. Thrombosis and Haemostasis. 2016;**115**(03):663-677

[21] Acebo E, Val-Bernal JF, Gomez-Roman JJ. Thrombomodulin, calretinin and c-kit (CD117) expression in cardiac myxoma. Histology and Histopathology. 2001;**16**(4):1031-1036

[22] Maleszewski JJ, Larsen BT, Kip NS, et al. PRKAR1A in the development of cardiac myxoma: A study of 110 cases including isolated and syndromic tumors. The American Journal of Surgical Pathology. 2014;**38**(8):1079-1087

[23] Wang Z, Chen S, Zhu M, et al. Risk prediction for emboli and recurrence of primary cardiac myxomas after resection. Journal of Cardiothoracic Surgery. 2016;**11**(22):1-8

[24] Reynen K. Cardiac myxomas. The New England Journal of Medicine. 1995;**333**(24):1610-1617

[25] Shinfeld A, Katsumata T, Westaby S. Recurrent cardiac myxoma: Seeding or multifocal disease? The Annals of Thoracic Surgery. 1998;**66**(1):285-288

[26] Fleischmann KE, Schiller NB. Papillary fibroelastoma: Move over myxoma. Journal of the American College of Cardiology. 2015;**65**(22):2430-2432

[27] Bicer M, Cikirikcioglu M, Pektok E, et al. Papillary fibroelastoma of the left atrial wall: A case report. Journal of Cardiothoracic Surgery. 2009;**4**(28):1-4

[28] Kurup AN, Tazelaar HD, Edwards WD, et al. Iatrogenic cardiac papillary fibroelastoma: A study of 12 cases (1990 to 2000). Human Pathology. 2002;**33**(12):1165-1169

[29] Remadi JP, Degandt A, Rakotoarivello Z. Cardiac papillary fibroelastoma of the mitral valve chordae. Heart. 2004;**90**:12

[30] Murphy ET. Robotic excision of aortic valve papillary fibroelastoma and concomitant maze procedure. Global Cardiology Science and Practice. 1 Nov 2013;**2012**(2):93-100. DOI: 10.5339/gcsp.2012.27. PubMed PMID: 24688994; PubMed Central PMCID: PMC3963717

[31] Grinda JM, Couetil JP, Chauvaud S, et al. Cardiac valve papillary fibroelastoma: Surgical excision for revealed or potential embolization. The Journal of Thoracic and Cardiovascular Surgery. 1999;**117**:106-110

[32] Klarich KW, Enriquez-Sarano M, Gura GM, et al. Papillary fibroelastoma: Echocardiographic characteristics for diagnosis and pathologic correlation. Journal of the American College of Cardiology. 1997;**30**(3):784-790

[33] Kamran H, Patel N, Singh G. Lambl's excrescences: A case report and review of the literature. Clinical Case Reports and Reviews. 2016;**2**(7):476-478

[34] Marstrand P, Jensen MB, Ihlemann N. Valvular excrescences: A possible transient phenomenon. Case Reports in Cardiology. 2015;**2015**:380765. DOI: 10.1155/2015/380765. Epub 2015 Nov 16

[35] Mkalaluh S, Szczechowicz M, Torabi S, Dib B, Sabashnikov A, Mashhour A, et al. Surgery for cardiac papillary fibroelastoma: A 12-year single institution experience. Medical Science Monitor Basic Research. 2017;**23**:258-263

[36] Shelh M. Multiplane transesophageal echocardiography detection of papillary fibroelastomas of the aortic valve causing a stroke. European Heart Journal. 1997;**18**(4):702-703

[37] Tamin SS, Maleszewski JJ, Scot CG, et al. Prognostic and bioepidemiologic implications of papillary fibroelastoma. Journal of the American College of Cardiology. 2015;**65**(22):2420-2429

[38] Sun JP, Asher CR, Yang S, et al. Clinical and echocardiographic characteristics of papillary fibroelastomas. A retrospective and prospective study in 162 patients. Circulation. 2001;**103**:2687-2693

[39] Abu Saleh WK, Al Jabbari O, Ramlawi B, Reardon MJ. Cardiac papillary fibroelastoma: Single-institution experience with 14 surgical patients. Texas Heart Institute Journal. 2016;**43**(2):148-151

[40] Mkalaluh S, Szczechowicz M, Torabi S, Dib B, Sabashnikov A, Mashhour A, et al. Surgery for cardiac papillary fibroelastoma: A 12-year single institution experience. Medical Science Monitor Basic Research. 2017;**23**:258

[41] Gowda RM, Khan IA, Nair CK, Mehta NJ, Vasavada BC, Sacchi TJ. Cardiac papillary fibroelastoma: A comprehensive analysis of 725 cases. American Heart Journal. 2003;**146**(3):404-410

[42] Klarich KW, Enriquez-Sarano M, Gura GM, Edwards WD, Tajik AJ, Seward JB. Papillary fibroelastoma: Echocardio-graphic characteristics for diagnosis and pathologic correlation. Journal of the American College of Cardiology. 1997;**30**(3):784-790

[43] Sabet A, Haghighiabyaneh M, Tazelaar H, Raisinghani A, DeMaria A. The clinical dilemma of cardiac fibroelastic papilloma. Structural Heart. 2018;**2**(4):274-280

[44] Li D, Wang W, Zhu Z, Wang Y, Xu R, Liu K. Cardiac lipoma in the interventricular septum: A case report. Journal of Cardiothoracic Surgery. Dec 2015;**10**(1):69

[45] Naseerullah FS, Javaiya H, Murthy A. Cardiac lipoma: An uncharacteristically large intra-atrial mass causing symptoms. Case Reports in Cardiology. 2018;**2018**:3531982

[46] Laeeq R, Merchant O, Khalid UM, Lakkis NM. Large cardiac lipoma in a patient presenting with atrial tachycardia and systolic heart failure. Journal of Cardiac Failure. 2017;**23**(8):S94

[47] Wijesurendra RS, Sheppard KA, Westaby S, Ormerod O, Myerson SG. The many faces of cardiac lipoma—An egg in the heart! European Heart Journal Cardiovascular Imaging. 2017;**18**(7):821

[48] Kim YS, Lee KH, Choi SJ, Baek WK. Cardiac lipoma arising from left ventricular papillary muscle: Resect or not? The Journal of Thoracic and Cardiovascular Surgery. 2018;**156**(1):244-246

[49] Dickerson JA, Smith M, Kalbfleisch S, Firstenberg MS. Lipomatous hypertrophy of the intraatrial septum resulting in right atrial inflow obstruction and atrial flutter. The Annals of Thoracic Surgery. 2010;**89**(5):1647-1649

[50] Shah DJ, Reardon MJ. Case of a hamartoma or hamartoma of a case? The Journal of Thoracic and Cardiovascular Surgery. 2018;**155**(1):351-352

[51] El-Ashry AA, Cerfolio RJ, Singh SP, McGiffin D. Cardiac paraganglioma. Journal of Cardiac Surgery. 2015;**30**(2):135-139

[52] Tudor AA, Tschui J, Schmidli J, Schmid RA, Dorn P. Cardiac paraganglioma—A rare subset of a rare tumor. World Journal of Cardiovascular Diseases. 2017;**7**:1-9

[53] Thompson KA. Managing benign cardiac tumors. MD Anderson Practices. Onco-Cardiology. 2016;**30**:30-35

[54] Sarjeant JM, Butany J, Cusimano RJ. Cancer of the heart: Epidemiology and management of primary neoplasms and metastases. American Journal of Cardiovascular Drugs. 2003;**3**:407-421

[55] Valente M, Cocco P, Thiene G, Casula R, Poletti A, Milanesi O, et al. Cardiac fibroma and heart transplantation. The Journal of Thoracic and Cardiovascular Surgery. 1993;**106**(6):1208-1212

[56] Cho JM, Danielson GK, Puga FJ, Dearani JA, McGregor CG, Tazelaar HD, et al. Surgical resection of ventricular cardiac fibromas: Early and late results. The Annals of Thoracic Surgery. 2003;**76**(6):1929-1934

[57] Yanagawa B, Mazine A, Chan EY, Barker CM, Gritti M, Reul RM, et al. Surgery for tumors of the heart. Seminars in Thoracic and Cardiovascular Surgery. 2018;**30**(4):385-397

[58] Luo C, Zhu J, Bao C, Ding F, Mei J. Minimally invasive and conventional surgical treatment of primary benign cardiac tumors. Journal of Cardiothoracic Surgery. 2019;**14**(1):76

[59] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. ESC/EACTS guidelines for the management of valvular heart disease. European Heart Journal. 2017;**38**(36):2739-2791

[60] Opolski MP, Staruch AD, Jakubczyk M, Min JK, Gransar H, Staruch M, et al. CT angiography for the detection of coronary artery stenoses in patients referred for cardiac valve surgery: Systematic review and meta-analysis. JACC: Cardiovascular Imaging. 2016;**9**(9):1059-1070

[61] Couture P, Denault AY, McKenty S, Boudreault D, Plante F, Perron R, et al. Impact of routine use of intraoperative transesophageal echocardiography during cardiac surgery. Canadian Journal of Anesthesia. 2000;**47**(1):20-26

[62] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, et al. AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Journal of the American College of Cardiology. 2017;**70**(2):252-289

[63] Ellouze M, Pellerin M, Jeanmart H, Lebon JS, Bouchard D. Mini right anterior thoracotomy approach versus sternotomy for resection of intracardiac myxoma. Innovations: Technology and Techniques in Cardiothoracic and Vascular Surgery. 2018;**13**(4):292-295

[64] Jain S, Maleszewski JJ, Stephenson CR, Klarich KW. Current diagnosis and management of cardiac myxomas. Expert Review of Cardiovascular Therapy. 2015;**13**(4):369-375

[65] Yuan SM. Infected cardiac myxoma: An updated review. Brazilian Journal of Cardiovascular Surgery. 2015;**30**(5):571-578

Chapter 4

Coronary Embolic Phenomena: High-Impact, Low-Frequency Events

Qasim Malik, Ambreen Alam, Stanislaw P. Stawicki and Peter Puleo

Abstract

Coronary embolic phenomena (CEP) are difficult to diagnose yet carry potentially devastating clinical consequences. The goal of this chapter is to outline key processes and pathophysiologic mechanisms underlying CEP, primarily in the context of acute coronary syndrome (ACS). Not surprisingly, most reported cases of CEP occur in the left coronary circulation, but some right-sided events have been reported. Overall, causes include thrombotic, septic/infectious, neoplastic, valve-related, and iatrogenic mechanisms such as air embolization. Coronary angiography remains the definitive diagnostic and therapeutic approach, with computed tomography being increasingly utilized. Transthoracic echocardiography (TTE) should be part of a routine work up for patients with suspected CEP. Holter/event monitoring for atrial fibrillation may also be indicated in patients with embolic phenomena. Clinical management includes procedural restoration of coronary blood flow, followed by appropriate anticoagulation or antiplatelet therapy, in conjunction with appropriate treatment of any arrhythmias or other associated cardiac manifestations or conditions. Timely diagnosis, based on a high index of suspicion (especially in high-risk population) may be important in improving morbidity and mortality in affected patients. Since CEPs are often underdiagnosed and may be due to a number of heterogeneous causes, the need arises for increasing provider awareness of these important phenomena, as well as for the implementation of appropriate clinical management guidelines.

Keywords: coronary artery embolism, coronary embolic phenomena, diagnosis, management, risk factors

1. Introduction

Coronary embolic phenomena (CEP) constitute an under-reported and underdiagnosed set of clinical phenomena, with potentially devastating consequences if not recognized and treated promptly [1–3]. From coronary air embolism to paradoxical venous thromboembolism, CEPs represent an etiologically heterogeneous group of events [4–7]. It has been postulated that CEPs are the underlying cause of up to 3% of acute coronary syndromes (ACS) [6]. Given their rarity, CEPs require a high index of suspicion by the treating clinician [8–10]. In this chapter, we will aim to cover the various processes and pathophysiology underlying this cause of acute coronary

syndrome. Our focus will be on the more commonly seen forms of coronary embolism, with an abbreviated overview provided of the less common etiologies.

2. Methods

A thorough literature search was conducted using PubMed, Google™ Scholar, and Bioline International. The following search terms were utilized, in various combinations/derivations/iterations, listed alphabetically: "cardiac," "coronary," "emboli," "embolism," "embolus," "heart," "infarction," "myocardial," "myocardium," "paradoxical," "phenomenon," "vascular," "vasculature," and "vessel". Secondary identification of additional literature sources was performed using articles referenced by our primary sources.

3. Classification

Coronary emboli may be classified based on etiology (i.e., thrombotic, septic, neoplastic, valvular heart disease-related, iatrogenic), although other classifications (i.e., direct, paradoxical and/or iatrogenic) have been proposed and/or described [6, 11–13]. A list of all previously reported types/causes of coronary emboli is provided in **Table 1**.

Thrombotic	Paradoxical thrombus/embolus
	Left atrial appendage thrombus
	Left atrial thrombus
	Left ventricular mural thrombus
Autoimmune	Inherited coagulation factor deficiencies (prothrombin deficiency, protein C/S deficiency)
	System lupus erythematosus
	Antiphospholipid syndrome
Infectious	Infective endocarditis
	Rheumatic heart disease
Valve-related	Fibroelastoma
	Mitral valve calcifications
	Blood cysts
Neoplastic	Malignancy
Iatrogenic	Post-cardiac procedure
Miscellaneous causes	Pregnancy
	Air embolism

Table 1.
Causes of coronary embolism.

4. Mechanisms and pathophysiology

Coronary emboli may originate in the left or right side of the heart [14, 15]. Of course, for emboli originating in the right heart to lodge in the coronary arteries, they would need to be somehow "shunted" to the left-sided system, possibly

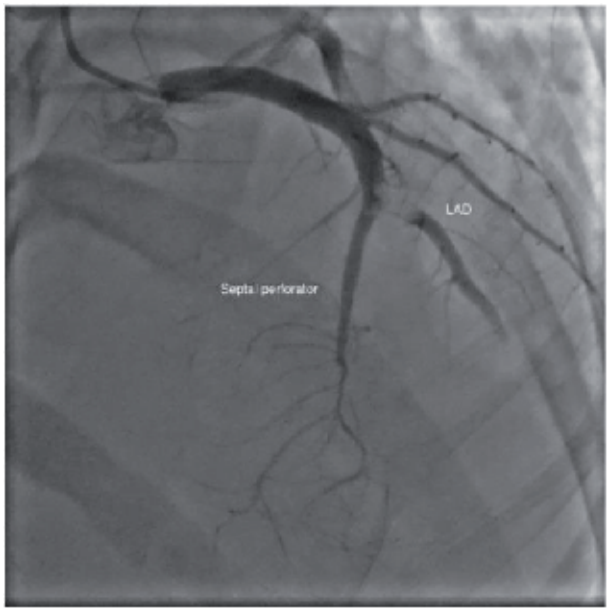

Figure 1.
Angiographic example of a large coronary artery embolus located in the mid-left anterior descending artery. Source: Zhang et al. [19]. Image used under the terms of the Creative Commons Attribution 4.0 License (http://www.creativecommons.org/licenses/by/4.0/) which permits any use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

through a patent foramen ovale [16–18]. An angiographic example of paradoxical coronary artery embolism is show in **Figure 1** [19].

It must be mentioned here that systemic emboli finding their way to the left heart are still more likely to embolize to the carotid or intracranial vasculature, primarily due to two particular considerations. Firstly, the coronary anatomy and coronary artery takeoff is typically such that emboli are less likely to specifically dislodge and enter into their ostia [13, 20, 21]. Secondly, it is hypothesized that coronary vessels may be protected to some degree, mainly due to them receiving flow primarily during diastole [22–26]. For similar reasons, one might extrapolate that most reported cases of coronary embolism occur in the left coronary circulation due to the anatomy of the right coronary artery takeoff making it potentially less conducive to emboli [22–28].

Coronary emboli may become lodged in major epicardial arteries supplying a sizable area of myocardium, and smaller emboli may even embolize distally so as to affect small arterioles which do not supply a large area [29–31]. These events may or may not be clinically symptomatic or readily diagnosable, but evidence in this generally poorly understood area of cardiac pathophysiology continues to be lacking. It is important to note, however, that coronary emboli may occur in the setting of concomitant atherosclerosis, where even a small embolus could lodge at the site of atherosclerotic lesion and result in significant epicardial coronary occlusion, thus exposing potentially significant area of myocardium at risk for a subsequent secondary ischemic event [31–35]. An association with infectious etiology may be present as well in this context [32].

5. Coronary embolic events: a heterogeneous pathologic grouping

Due to various mechanisms being responsible for coronary embolic phenomena leading to acute coronary syndromes, we will address them one by one in the

subsequent discussion. The authors' goal is not to provide an exhaustive description of each mechanism, but rather to point the reader to other definitive sources for further details.

5.1 Thrombotic causes

Coronary emboli may be formed due to thromboembolic causes involving different etiologies and pathways (**Table 1**). As with all thromboembolic phenomena, predisposing conditions of the Virchow's triad (hypercoagulability, stasis, endothelial injury) will need to be present for thrombi to form [36, 37].

For venous thromboemboli to "transform" into coronary emboli, the presence of a patent foramen ovale is required [6, 38]. This enables the embolus to cross from "right to left" side of the heart and thus develop the potential to lodge in the coronary circulation [18, 38]. A thrombus may originate in the left atrial appendage, as seen among patients with atrial fibrillation [39, 40], or it may originate in the left atrium/ventricle itself, as in patients with severely reduced ejection fraction or those who have had an anterior/apical myocardial infarction in the past [6, 41]. The former is of particular clinical importance, as patients diagnosed with coronary embolus may benefit from ambulatory monitoring to look for atrial fibrillation as a possible underlying cause.

Arterial emboli are more likely to be reported in the setting of hypercoagulable states including autoimmune diseases, inherited coagulation factor deficiencies, hyperviscosity syndromes, and acquired hypercoagulabe states (e.g., pregnancy, malignancy, previous heparin exposure, **Table 1**) [42–44]. As coronary emboli are a rarely reported phenomenon, no randomized trials or guidelines exist regarding diagnostic workup for these, although it would not be unreasonable to initiate workup for thrombophilia whenever appropriate diagnosis or suspicion exists [37, 42–45].

5.2 Septic/infectious causes

Infective endocarditis is one of the most dreaded infectious etiologies associated with significant morbidity and mortality [46, 47]. Coronary septic arterial emboli (CSAE) secondary to infectious endocarditis have been reported and according to one source such events may carry a mortality of up to 50% [48]. CSAE appear to be more likely to occur in patients having vegetations of the mitral valve or fungal infections, as fungal vegetations are known to reach larger overall dimensions, thus increasing the cumulative possibility of embolization [49, 50]. Rheumatic heart disease, though more common in low-income countries, is another possible etiology that can be associated with CSAE and must be kept in mind when evaluating patients from high-incidence geographic areas [51, 52].

5.3 Neoplastic causes

Tumors originating in the heart such as atrial myxomas, or on valves such as papillary fibroelastomas, are well known to cause cryptogenic brain infarctions [14, 53]. There are also reports of embolization to the coronary circulation [54–56]. Given that end-organ damage, including cerebrovascular accidents may constitute the initial clinical presentation of such neoplasms, it would not be unreasonable to propose that an embolic myocardial infarction may occur in this setting [56, 57]. It is also likely that such occurrences are under-recognized and probably more common than generally thought, thus requiring high index of clinical suspicion and prompt diagnosis [56, 57]. The overall urgency is highlighted by the possibility that subsequent presentations in cases of "missed diagnosis" may manifest as unexplained/

sudden death [57, 58]. Appropriate high-quality imaging may include but is not limited to transthoracic and/or transesophageal echocardiography [56, 59–61].

5.4 Valve-related causes

Stenotic heart valves resulting from progressive calcification process also pose the possibility of calcific embolization to distal locations, including the coronary circulation [48, 62, 63]. Rheumatic valvular heart disease could be another possible risk factor for coronary embolization [48]. Long-term valvular heart disease leads to structural changes in the myocardium, eventually increasing the risk of atrial fibrillation, which in itself may be a contributor to both systemic and coronary embolization [39, 64]. Of note, coronary embolism has been reported following aortic and mitral valve replacement, with successful management reported to involve abciximab and urokinase [65]. Another report describes acute myocardial infarction due to coronary embolism in a patient with mitral valve prosthesis. That particular case was successfully managed using angioplasty [66]. An example of a left coronary embolism associated with subtherapeutic oral anticoagulation in a patient with mitral and aortic mechanical valve prostheses is shown in **Figure 2** [67].

5.5 Iatrogenic causes

Ruptured atherosclerotic plaques in the coronary arteries may lead to acute thrombotic occlusions and are the frequent pathophysiologic factor behind acute ST-elevation myocardial infarctions [68, 69]. Vessels affected by such processes may be characterized by a high thrombotic burden. For example, saphenous venous grafts in post-coronary artery bypass graft patients seem particularly vulnerable [70, 71], with various pathophysiologic mechanisms proposed including immune-mediated process [71, 72].

Cardiac catheterization procedures may also cause distal embolization of intravascular particles [73]. Depending upon where, and how far, any dislodged thrombi or microthrombi travel, periprocedural myocardial infarction can become a very real risk [74]. Various procedural techniques including specialized "wire filter" protection devices [74, 75] and thrombus extraction catheters [76] can be utilized during coronary interventions to prevent or reduce distal embolization. Finally,

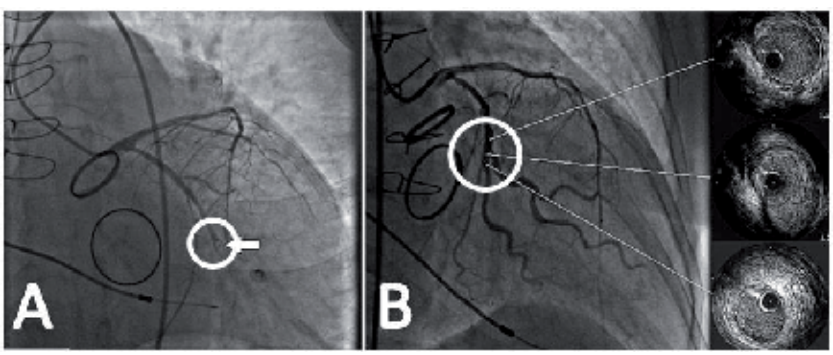

Figure 2.
An example of a left coronary artery coronary embolism associated with subtherapeutic anticoagulation in the setting of mitral and aortic mechanical valve prostheses. [A, left] Note the filling defect present upon initial diagnosis. [B, right] Following thrombectomy, the left coronary artery is seen to be patent. Source: Protasiewicz et al. [67]. Images used under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License, which permits all noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

distal coronary embolization involving cholesterol particles is also a possibility in patients undergoing diagnostic coronary angiography or thrombolysis [77, 78].

6. Diagnosis of coronary embolism

A careful history and physical examination is necessary, with specific focus on finding any systemic signs of emboli in septic patients, as well as the possibility of an autoimmune disease in the subset of non-septic patients [79–81]. As with suspected coronary artery disease, patients suffering from coronary embolism may present with typical or atypical chest pain or with "angina equivalents" such as dyspnea [79, 81, 82]. As with all acute coronary syndromes, electrocardiography will be very important in determining the diagnosis and may dictate the urgency for cardiac catheterization (e.g., the presence of ST-elevation myocardial infarction). The presence of Q-waves in contiguous leads may be indicative of a "silent" myocardial infarction. Troponin and other cardiac enzyme testing certainly plays an important role in determining the extent and the progression of myocardial ischemia [83, 84]. Subsequent workup should include transthoracic and transesophageal echocardiography, advanced high-resolution imaging (e.g., CT or MRI), and coronary angiography [18, 85–87]. In addition, miscellaneous adjunctive diagnostic tools, such as Holter/event monitoring, can also be helpful in cases where etiology of the event(s) in question may be uncertain [88, 89].

6.1 Coronary angiography

Coronary angiography remains the mainstay of CEP diagnostics [87]. As outlined previously, patients affected by this condition may have "silent" myocardial infarction or may present with an acute ST segment elevation myocardial infarction. When performing angiography, associated thrombi have a distinct hazy angiographic appearance [87, 90, 91]. Moreover, angiography can help document the evolution and resolution of coronary embolism [92]. Finally, diagnostic angiography can be converted into a therapeutic procedure if indicated [87, 93].

The angiographer should keep in mind that the presence of multiple acute thromboembolic lesions in various vessels increases the suspicion for embolic coronary phenomena [94]. As mentioned above, these emboli may also acutely occlude parts of vessels with pre-existing atherosclerosis, further complicating the diagnosis. Intravascular ultrasound following aspiration atherectomy may be useful when assessing for underlying atherosclerosis versus purely acute thromboembolic phenomena. Optical coherence tomography of these vessels may also be useful but has not yet been studied sufficiently in this particular setting [95, 96]. A patient with angiographic evidence of coronary embolism but with no traditional risk factors for coronary artery disease should raise the suspicion for some of the less common causes (e.g., autoimmune, infectious, inflammatory, or neoplastic) [6, 94, 97].

After diagnostic confirmation, coronary thrombi are often removed using aspiration catheters, as outlined in previous paragraphs. Biopsy of these specimens would aid in differentiating between thrombotic, septic, and neoplastic causes of embolism, particularly due to the fact that these may be the presenting events in some neoplasms. Autoimmune disease may also need to be ruled out [6, 94, 97].

6.2 Transthoracic echocardiography

Transthoracic echocardiography should be a part of the routine workup for patients with suspected CEP. Diagnostically, it will be critically important to

demonstrate or rule out the presence of patent foramen ovale [98–100] and identify any thrombi in left-sided cardiac chambers, particularly with the help of ultrasonic contrast [33, 59]. Any suspicion should be further supplemented with transesophageal echocardiography to ascertain any transthoracic echocardiography findings, especially those of uncertain significance or insufficiently granular detail(s) [59, 101]. In addition, this would also be helpful to visualize the left atrial appendage when looking for evidence of either stasis or thrombus formation there [102, 103]. Such findings can be present in the setting of atrial fibrillation [102].

As outlined earlier in this manuscript, Holter/event monitoring to look for atrial fibrillation would also be reasonable in patients being seen for embolic phenomena [88, 89]. As for all thromboembolic diseases, thrombophilia workup would also be useful in ascertaining the etiology of coronary embolism in appropriately selected at-risk patients [104].

7. Clinical management

Coronary embolic syndromes are quite heterogeneous, and lack randomized controlled trial data or specific guidelines on their management. The initial approach including timing of cardiac catheterization for coronary embolism should be the same as for routine acute coronary syndrome (with classification of available evidence quality provided in parentheses) [106].

Oxygen (Class 1), nitrates (Class 1), and beta blockers (Class 1) are the mainstay of the initial medical management [106] in addition to parenteral anticoagulation (Enoxaparin/unfractionated heparin [UHF]/Bivalirudin) [109].

Decision regarding the use of percutaneous coronary intervention versus balloon angioplasty would be up to the clinician's judgment given plaque morphology as assessed by intravascular ultrasound as well as on optical coherence tomography.

Following the initial management, dual antiplatelet inhibition would be recommended for these patients [107] for a duration of 6–12 months as per the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines [108].

As no randomized controlled data are available on lipid management for the particular subset of patients suffering from coronary embolism, we would recommend following current society guidelines for lipid management in these patients.

For patients with reduced ejection fraction on echocardiography, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers in addition to aldosterone antagonists are recommended (Class 1) [106, 109].

Long-term anticoagulation in patients diagnosed with embolic coronary disease remains a question to be answered. As with other embolic phenomena, 3–6 months of anticoagulation with warfarin or with direct anticoagulants would be reasonable, with further therapy to be decided upon ascertaining the underlying etiology.

Workup to determine the etiology is essential, and treatment of the cause of embolism is of course necessary. As mentioned above, remote cardiac monitoring to look for atrial fibrillation is essential as it may necessitate lifelong anticoagulation particularly in patients with high CHADS2VASC scores.

Lastly, in patients possibly requiring triple antithrombotic therapy, data are limited, with current management approaches based on consensus recommendations with only a brief mention in the 2016 ACC Guidelines [108]. The decision regarding the duration or discontinuation of triple therapy versus P2Y12 inhibitor plus vitamin K antagonists (VKA)/direct oral anticoagulants (DOAC) would be based on the individualized bleeding risk versus the potential risk of discontinuing these medicines [108].

8. Miscellaneous causes

It has been reported that air embolism can complicate a variety of invasive procedures involving the vasculature, from central venous access placement to coronary artery bypass grafting [105, 106]. In the context of CEPs, the presence of patent foramen ovale (PFO) plays an important contributory role [107]. Though rarely reported, air embolism due to decompression illnesses or due to iatrogenic causes may also cause coronary embolism. Finally, iatrogenic CEPs are fortunately uncommon, yet they are dreaded events that may occur in the cardiac catheterization lab or during coronary artery bypass graft (CABG) surgery [103, 104].

Amniotic fluid embolism (AFE) in pregnant women can also lead to coronary embolization [105, 108]. Of note, for amniotic fluid to embolize to the coronary arteries, the patient must also have a PFO which helps facilitate the right-to-left transit of causative particles, which then lodge in the systemic arterial system and, potentially, the coronary arteries. It has been noted that the appearance of amniotic fluid emboli in the coronary circulation may be associated with elevated mortality when compared with cases not involving the coronary vessels [108]. Marked constriction of coronary arteries has also been described in the setting of AFE, although it is not known if that is a direct or an indirect effect [109, 110].

9. Conclusion

Coronary embolic phenomena are a heterogeneous group of clinicopathologic entities attributable to a variety of etiologic factors. Due to their rarity and the tendency to clinically mimic other coronary syndromes, CEPs are often underdiagnosed. Timely diagnosis using an elevated index of suspicion in high-risk patients is important to improving the associated morbidity and mortality. Scarcity of high quality data regarding CEPs necessitates further studies and dedicated consensus guidelines. Progress in diagnosis and treatment of CEPs will require concerted efforts by clinicians, educators, and researchers.

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References

[1] De Filippo M, Capasso R. Coronary computed tomography angiography (CCTA) and cardiac magnetic resonance (CMR) imaging in the assessment of patients presenting with chest pain suspected for acute coronary syndrome. Annals of Translational Medicine. 2016;**4**(13):255

[2] Jin M-F, Xu Z. Delayed post-dilated stenting to treat an embolic myocardial infarction. Journal of Geriatric Cardiology: JGC. 2016;**13**(10):872

[3] Kei J, Avilla JK, Cavendish JJ. Rare case of myocardial infarction in a 19-year-old caused by a paradoxical coronary artery embolism. The Permanente Journal. 2015;**19**(2):e107

[4] White PD. The epidemiology of heart disease. Irish Journal of Medical Science (1926-1967). 1957;**32**(10):426-440

[5] Khan M et al. Coronary air embolism: Incidence, severity, and suggested approaches to treatment. Catheterization and Cardiovascular Diagnosis. 1995;**36**(4):313-318

[6] Raphael CE et al. Coronary embolus: An underappreciated cause of acute coronary syndromes. JACC: Cardiovascular Interventions. 2018;**11**(2):172-180

[7] Meier-Ewert HK et al. Paradoxical embolism in the left main coronary artery: Diagnosis by transesophageal echocardiography. In: Mayo Clinic Proceedings. New York, New York: Elsevier. 2003;**78**(1):103-106

[8] Zeller L et al. A rare complication of infective endocarditis: Left main coronary artery embolization resulting in sudden death. Journal of Heart Valve Disease. 2010;**19**(2):225

[9] Reid CL, Elkayam U, Rahimtoola SH. Infective endocarditis in pregnancy. In: Principles of Medical Therapy in Pregnancy. New York, New York: Springer; 1985. pp. 671-679

[10] Apostol-Alday AS, Ganzon MS. Coronary embolism causing ST elevation myocardial infarction complicated by ventricular septal rupture. Philippine Journal of Internal Medicine. 2016;**54**(3):1-5

[11] Meister SG et al. Paradoxical embolism: Diagnosis during life. The American Journal of Medicine. 1972;**53**(3):292-298

[12] Hillis LD, Cohn PF. Nonatherosclerotic coronary artery disease. In: Diagnosis and Therapy of Coronary Artery Disease. Boston, Massachusetts: Springer; 1985. pp. 495-505

[13] Glazier JJ, Mcginnity JG, Spears JR. Coronary embolism complicating aortic valve endocarditis: Treatment with placement of an intracoronary stent. Clinical Cardiology. 1997;**20**(10):885-888

[14] Stoane L, Allen JH Jr, Collins HA. Radiologic observations in cerebral embolization from left heart myxomas. Radiology. 1966;**87**(2):262-266

[15] Waller B et al. Nonatherosclerotic causes of coronary artery narrowing—Part II. Clinical Cardiology. 1996;**19**(7):587-591

[16] Conti CR. Are "paradoxical emboli" really paradoxical? Clinical Cardiology: An International Indexed and Peer-Reviewed Journal for Advances in the Treatment of Cardiovascular Disease. 2003;**26**(3):105-106

[17] Corrin B. Paradoxical embolism. British Heart Journal. 1964;**26**(4):549

[18] Dao CN, Tobis JM. PFO and paradoxical embolism producing events other than stroke. Catheterization and Cardiovascular Interventions. 2011;**77**(6):903-909

[19] Zhang J et al. Successful implementation of extracorporeal membrane oxygenation support as a bridge to heart-lung transplantation in an Eisenmenger's syndrome patient with paradoxical coronary embolism. Journal of Investigative Medicine High Impact Case Reports. 2019;**7**:2324709619846575

[20] Sampson B, Hammers J. Forensic aspects of cardiovascular pathology. In: Cardiovascular Pathology. Cambridge, Massachusetts: Academic Press/ Elsevier; 2016. pp. 773-798

[21] Capodanno D et al. Epidemiology and clinical impact of different anatomical phenotypes of the left main coronary artery. Heart and Vessels. 2011;**26**(2):138-144

[22] Bolger AF et al. Transit of blood flow through the human left ventricle mapped by cardiovascular magnetic resonance. Journal of Cardiovascular Magnetic Resonance. 2007;**9**(5):741-747

[23] Verani MS et al. Quantification of left ventricular performance during transient coronary occlusion at various anatomic sites in humans: A study using tantalum-178 and a multiwire gamma camera. Journal of the American College of Cardiology. 1992;**19**(2):297-306

[24] Kim H et al. Patient-specific modeling of blood flow and pressure in human coronary arteries. Annals of Biomedical Engineering. 2010;**38**(10):3195-3209

[25] Chaichana T, Sun Z, Jewkes J. Computation of hemodynamics in the left coronary artery with variable angulations. Journal of Biomechanics. 2011;**44**(10):1869-1878

[26] Yamanaka O, Hobbs RE. Coronary artery anomalies in 126,595 patients undergoing coronary arteriography. Catheterization and Cardiovascular Diagnosis. 1990;**21**(1):28-40

[27] Hirono K et al. Anomalous origin of the right coronary artery evaluated with multidetector computed tomography and its clinical relevance. Journal of Cardiology. 2016;**68**(3):196-201

[28] Kimbiris D et al. Anomalous aortic origin of coronary arteries. Circulation. 1978;**58**(4):606-615

[29] Niccoli G et al. Microvascular obstruction after primary percutaneous coronary intervention: Pathogenesis, diagnosis and prognostic significance. Current Vascular Pharmacology. 2013;**11**(2):245-262

[30] Groskloss HH. Fat embolism. The Yale Journal of Biology and Medicine. 1935;**8**(1):59

[31] Chandler A. Mechanisms and frequency of thrombosis in the coronary circulation. Thrombosis Research. 1974;**4**:3-23

[32] Greenstein J. Sudden death from cardiac and aortic disease. South African Medical Journal. 1947;**21**(9):307-320

[33] Kotooka N et al. Three cases of acute myocardial infarction due to coronary embolism. Japanese Heart Journal. 2004;**45**(5):861-866

[34] Waller BF et al. Embolus to the left main coronary artery. American Journal of Cardiology. 1982;**50**(3):658-660

[35] Charles R, Epstein E. Diagnosis of coronary embolism: A review. Journal of the Royal Society of Medicine. 1983;**76**(10):863-869

[36] Malone P, Agutter P. The aetiology of deep venous thrombosis. Journal

of the Association of Physicians. 2006;**99**(9):581-593

[37] Prosciak MP, Stawicki SP. Hypercoagulable states: A concise review. International Journal of Academic Medicine. 2017;**3**(3):82

[38] Bennett J, Ong L, Hanratty C. Paradoxical coronary embolism, a rare cause of acute myocardial infarction on positive pressure ventilation. Acta Cardiologica. 2012;**67**(4):477-479

[39] Van de Walle S, Dujardin K. A case of coronary embolism in a patient with paroxysmal atrial fibrillation receiving tamoxifen. International Journal of Cardiology. 2007;**123**(1):66-68

[40] Kuramoto K, Matsushita S, Yamanouchi H. Atrial fibrillation as a cause of myocardial and cerebral infarctions: Symposium on clinical aspects of thromboembolism. Japanese Circulation Journal. 1984;**48**(1):67-74

[41] Zachura M et al. Acute myocardial infarction due to coronary embolism originating from left ventricle thrombus in a patient with dilated cardiomyopathy and sinus rhythm. Postepy w Kardiologii Interwencyjnej. 2016;**12**(1):73

[42] Acharya SS, Sarangi SN. Disorders of coagulation. In: Lanzkowsky's Manual of Pediatric Hematology and Oncology. Cambridge, Massachusetts: Academic Press/Elsevier; 2016. pp. 279-333

[43] Silva A et al. Thrombophilia/ prothrombotic disorders. Sociedade Portuguesa de Medicină Internă. 2010;**17**:1

[44] Barelli S, Blum S, Angelillo-Scherrer A. Acquired hemostatic disorders. In: Perioperative Hemostasis. Berlin, Heidelberg: Springer; 2015. pp. 89-108

[45] Quarrie R, Stawicki SP. Portal vein thrombosis: What surgeons need to know. International Journal of Critical Illness and Injury Science. 2018;**8**(2):73

[46] Wojda TR et al. Septic embolism: A potentially devastating complication of infective endocarditis. In: Contemporary Challenges in Endocarditis. Rijeka: IntechOpen; 2016

[47] Stawicki SP et al. Septic embolism in the intensive care unit. International Journal of Critical Illness and Injury Science. 2013;**3**(1):58

[48] Charles R et al. Coronary embolism in valvular heart disease. QJM: An International Journal of Medicine. 1982;**51**(2):147-161

[49] Adams PC et al. Thrombosis and embolism from cardiac chambers and infected valves. Journal of the American College of Cardiology. 1986;**8**(6 Supplement 2):76B-87B

[50] Kothari S, Ramakrishnan S, Bahl V. Infective endocarditis—An Indian perspective. Indian Heart Journal. 2005;**57**(4):289

[51] Wartman WB, Hellerstein HK. The incidence of heart disease in 2,000 consecutive autopsies. Annals of Internal Medicine. 1948;**28**(1):41-65

[52] Lee Shrader E, Bawell M, Moragues V. Coronary embolism. Circulation. 1956;**14**(6):1159-1163

[53] Mikati I, Ibrahim Z. Cardioembolic Stroke. Warlow's Stroke: Practical Management. 2019. pp. 241-265

[54] Inman W, Vessey M. Investigation of deaths from pulmonary, coronary, and cerebral thrombosis and embolism in women of child-bearing age. British Medical Journal. 1968;**2**(5599):193

[55] Braun S et al. Myocardial infarction as complication of left atrial myxoma. International Journal of Cardiology. 2005;**101**(1):115-121

[56] Hashimoto H et al. Acute myocardial infarction due to coronary embolization from left atrial myxoma. Japanese Circulation Journal. 1993;**57**(10):1016-1020

[57] Burke AP, Virmani R. Cardiac myxoma: A clinicopathologic study. American Journal of Clinical Pathology. 1993;**100**(6):671-680

[58] Edwards FH et al. Primary cardiac valve tumors. The Annals of Thoracic Surgery. 1991;**52**(5):1127-1131

[59] Ward R, Jones D, Haponik EF. Paradoxical embolism: an underrecognized problem. Chest. 1995;**108**(2):549-558

[60] Mousavi N et al. Assessment of cardiac masses by cardiac magnetic resonance imaging: Histological correlation and clinical outcomes. Journal of the American Heart Association. 2019;**8**(1):e007829

[61] Young PM et al. Computed tomography imaging of cardiac masses. Radiologic Clinics. 2019;**57**(1):75-84

[62] Johnson D, Gonzalez-Lavin L. Myocardial infarction secondary to calcific embolization: An unusual complication of bioprosthetic valve degeneration. The Annals of Thoracic Surgery. 1986;**42**(1):102-103

[63] Pantely GA et al. Monocular blindness secondary to calcific embolization: An unusual presentation of rheumatic mitral valvular disease. Chest. 1976;**69**(4):555-556

[64] Soliman EZ et al. Atrial fibrillation and the risk of myocardial infarction. JAMA Internal Medicine. 2014;**174**(1):107-114

[65] Quinn EG, Fergusson DJ. Coronary embolism following aortic and mitral valve replacement: Successful management with abciximab and urokinase. Catheterization and Cardiovascular Diagnosis. 1998;**43**(4):457-459

[66] Sial JA et al. Coronary embolism causing acute myocardial infarction in a patient with mitral valve prosthesis: Successful management with angioplasty. JPMA. The Journal of the Pakistan Medical Association. 2009;**59**(6):409

[67] Protasiewicz M et al. Cardiac arrest due to left circumflex coronary artery embolism as a complication of subtherapeutic oral anticoagulation in a patient with mitral and aortic mechanical valve prostheses. Postępy w Kardiologii Interwencyjnej = Advances in Interventional Cardiology. 2013;**9**(1):97

[68] Bertrand M et al. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. European Heart Journal. 2002;**23**:1809-1840

[69] Lerman A et al. Microcirculatory dysfunction in ST-elevation myocardial infarction: Cause, consequence, or both? European Heart Journal. 2007;**28**(7):788-797

[70] Walts AE, Fishbein MC, Matloff JM. Thrombosed, ruptured atheromatous plaques in saphenous vein coronary artery bypass grafts: Ten years' experience. American Heart Journal. 1987;**114**(4):718-723

[71] Walts A et al. Ruptured atheromatous plaques in saphenous vein coronary artery bypass grafts: A mechanism of acute, thrombotic, late graft occlusion. Circulation. 1982;**65**(1):197-201

[72] Ratliff N, Myles J. Rapidly progressive atherosclerosis in aortocoronary saphenous vein grafts. Possible immune-mediated disease. Archives of Pathology & Laboratory Medicine. 1989;**113**(7):772-776

[73] Okamura A et al. Detection of embolic particles with the Doppler guide wire during coronary intervention in patients with acute myocardial infarction: Efficacy of distal protection device. Journal of the American College of Cardiology. 2005;**45**(2):212-215

[74] Taguchi I et al. Comparison of the effects of a distal embolic protection device and an aspiration catheter during percutaneous coronary intervention in patients with acute myocardial infarction. Circulation Journal. 2005;**69**(1):49-54

[75] Nakamura T et al. Effects of a distal protection device during primary stenting in patients with acute anterior myocardial infarction. Circulation Journal. 2004;**68**(8):763-768

[76] Lim MJ et al. Use of a new thrombus extraction catheter (the Pronto®) in the treatment of acute myocardial infarction. Journal of Interventional Cardiology. 2005;**18**(3):189-192

[77] Colt HG et al. Cholesterol emboli after cardiac catheterization. Eight cases and a review of the literature. Medicine. 1988;**67**(6):389-400

[78] Fukumoto Y et al. The incidence and risk factors of cholesterol embolization syndrome, a complication of cardiac catheterization: A prospective study. Journal of the American College of Cardiology. 2003;**42**(2):211-216

[79] Stokes J, Dawber TR. The silent coronary: The frequency and clinical characteristics of unrecognized myocardial infarction in the Framingham study. Annals of Internal Medicine. 1959;**50**(6):1359-1369

[80] Riboldi P et al. Cardiac involvement in systemic autoimmune diseases. Clinical Reviews in Allergy & Immunology. 2002;**23**(3):247-261

[81] Taniike M et al. Acute myocardial infarction caused by a septic coronary embolism diagnosed and treated with a thrombectomy catheter. Heart. 2005;**91**(5):e34-e34

[82] Braunwald E et al. Diagnosing and managing unstable angina. Agency for Health Care Policy and Research. Circulation. 1994;**90**(1):613-622

[83] Reichlin T et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. New England Journal of Medicine. 2009;**361**(9):858-867

[84] Keller T et al. Serial changes in highly sensitive troponin I assay and early diagnosis of myocardial infarction. JAMA. 2011;**306**(24):2684-2693

[85] Wintersperger B et al. Tumors of the cardiac valves: Imaging findings in magnetic resonance imaging, electron beam computed tomography, and echocardiography. European Radiology. 2000;**10**(3):443-449

[86] Rajiah P et al. MR imaging of myocardial infarction. Radiographics. 2013;**33**(5):1383-1412

[87] Hernández F et al. Acute coronary embolism: Angiographic diagnosis and treatment with primary angioplasty. Catheterization and Cardiovascular Interventions. 2002;**55**(4):491-494

[88] Watanabe K-i et al. Efficacy of amlodipine besilate therapy for variant angina: Evaluation by 24-hour Holter monitoring. Cardiovascular Drugs and Therapy. 1993;**7**(6):923-928

[89] Przybojewski J. Acute Transmural Myocardial Infarction-Coronary Vasospasm, Thrombosis or Coronary Embolus? A Case Report. South African Medical Journal. 1984;**66**:658-662

[90] Harlan JL, Meng RL. Thrombosis of the left main coronary artery following

percutaneous transluminal coronary angioplasty. The Annals of Thoracic Surgery. 1987;**43**(2):220-223

[91] Saito S et al. Primary stent implantation without coumadin in acute myocardial infarction. Journal of the American College of Cardiology. 1996;**28**(1):74-81

[92] Richardson P, Gotsman M. Angiographic evidence of coronary embolism and resolution. South African Medical Journal. 1971;**45**(7):805-809

[93] Xu B, Williams P, Burns AT. Acute myocardial infarction due to coronary artery embolus associated with atrial fibrillation. Acute Cardiac Care. 2013;**15**(4):93-95

[94] Schuster EH et al. Multiple coronary thromboses in previously normal coronary arteries: A rare cause of acute myocardial infarction. American Heart Journal. 1980;**99**(4):506-509

[95] Farooq MU et al. The role of optical coherence tomography in vascular medicine. Vascular Medicine. 2009;**14**(1):63-71

[96] Kume T et al. Assessment of coronary arterial thrombus by optical coherence tomography. The American Journal of Cardiology. 2006;**97**(12):1713-1717

[97] Tun A, Khan IA. Acute myocardial infarction with angiographically normal coronary arteries. Heart & Lung. 2000;**29**(5):348-350

[98] Gersony DR et al. Acute myocardial infarction caused by paradoxical coronary embolization in a patient with a patent foramen ovale. Journal of the American Society of Echocardiography. 2001;**14**(12):1227-1229

[99] Bridges ND et al. Transcatheter closure of patent foramen ovale after presumed paradoxical embolism. Circulation. 1992;**86**(6):1902-1908

[100] Speechly-Dick M, Middleton S, Foale R.Impending paradoxical embolism: A rare but important diagnosis. Heart. 1991;**65**(3):163-165

[101] Lee RJ et al. Enhanced detection of intracardiac sources of cerebral emboli by transesophageal echocardiography. Stroke. 1991;**22**(6):734-739

[102] Kato H et al. Evaluation of left atrial appendage stasis in patients with atrial fibrillation using transesophageal echocardiography with an intravenous albumin-contrast agent. American Journal of Cardiology. 1996;**78**(3):365-369

[103] García-Fernández MA et al. Left atrial appendage Doppler flow patterns: Implications on thrombus formation. American Heart Journal. 1992;**124**(4):955-961

[104] Vendittelli PS et al. Coronary artery embolism: Two case reports and a review of the literature. The American Journal of the Medical Sciences. 2018;**357**(4):333-337

[105] Rovai D et al. Gaseous coronary embolism as a cause of myocardial ischemia during coronary artery bypass grafting. The American Journal of Cardiology. 1995;**75**(4):282-285

[106] Evans D et al. Complications associated with pulmonary artery catheters: A comprehensive clinical review. Scandinavian Journal of Surgery. 2009;**98**(4):199-208

[107] Arnott C et al. Paradoxical cardiac and cerebral arterial gas embolus during percutaneous lead extraction in a patient with a patent foramen ovale. Heart, Lung and Circulation. 2015;**24**(1):e14-e17

[108] Morgan M. Amniotic fluid embolism. Anaesthesia. 1979;**34**(1):20-32

[109] Azegami M, Mori N. Amniotic fluid embolism and leukotrienes. American Journal of Obstetrics and Gynecology. 1986;**155**(5):1119-1124

[110] Locksmith GJ. Amniotic fluid embolism. Obstetrics and Gynecology Clinics of North America. 1999;**26**(3):435-444

Chapter 5

Acute Arterial Embolism of the Lower Limb

André Luís Foroni Casas

Abstract

Despite advances in the management of peripheral arterial occlusive disease, acute embolism of the lower extremities is still characterized by an important limb threat, morbidity, mortality, and continues to pose a challenge to the vascular surgeon. Atrial fibrillation, left ventricular aneurysm, penetrating ulcers or aneurysms of the aorta and common iliac arteries are the common sources of emboli. The presence of occlusion can be determined noninvasively with the use of duplex Doppler ultrasonography. Arteriography, Computed Tomographic Angiography and Magnetic Resonance Angiography can also be employed. Embolectomy is the standard for acute leg ischemia in patients with a strong clinical suspicion of an embolus, but alternative techniques, such as catheter-directed thrombolysis or percutaneous aspiration thrombolectomy, expand the role of radiologic percutaneous therapy of the acutely ischemic limb.

Keywords: thrombosis, embolism, embolectomy, fibrinolysis, lower extremity

1. Introduction

Acute limb ischemia results from a sudden decrease in limb perfusion that threatens limb viability and often requires urgent revascularization [1]. Acute ischemia of the lower limb continues to pose a challenge to the vascular surgeon and is still characterized by an important morbidity, limb threat and mortality. The two principal etiologies of acute ischemia of the lower limbs are arterial embolism and in situ thrombosis of an atherosclerotic artery or of a bypass graft [2]. It is estimated that the incidence of acute limb ischemia in the general population is around 14/100,000 inhabitants per year [3].

The consequences of acute limb ischemia such as prolonged hospitalization, major limb amputation, and/or death have a profound socioeconomic impact. Acute limb ischemia represents a high-risk cohort in need of complex revascularization procedures that are often associated with a significant rate of periinterventional complications [4]. Historic rates of amputation and mortality range from 10 to 25%, emphasizing the need for prompt evaluation and treatment [5, 6].

Embolism is the result of material passing through the arterial tree and obstructing a peripheral artery [7]. These materials may be thrombi, fragments of atheromatous plaque, tumor cells, or other foreign bodies, that have been dislodged or introduced into any part of the arterial system and can cause partial or total occlusion of an artery at a point distant from where they originated [8].

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The arteries most commonly affected in the lower limbs are the femoral, the popliteal, the iliac, and the aorta [9–13]. The most frequent site of involvement is the femoral bifurcation, accounting for 35–50% of cases [14–17].

The approach of the arterial embolism of the lower limb has evolved significantly in the past decade, especially regarding the development of endovascular treatment.

2. Etiology

The heart has been described as a source of emboli with frequency in the range of 78–96% [12, 18]. When emboli originate in the heart, more than 70% will obstruct the lower limbs, including those lodged at the bifurcation of the aorta [19]. The majority of emboli originate in the heart, primarily the left heart, as a result of fragmentation of intracavitary thrombi [15, 16].

Atrial fibrillation, left ventricular aneurysm, penetrating ulcers or aneurysms of the aorta and common iliac arteries are the common sources of emboli. Nearly all emboli arise from the left heart, aorta, and iliac vessels. A minority are paradoxical venous emboli that pass through an intracardiac shunt. Emboli typically lodge at branch points in the vascular tree and occlude both tributaries [20]. The most frequent cause of formation of these thrombi is atrial fibrillation, which occurs in mitral valve lesions of rheumatic origin, hyperthyroidism, acute myocardial infarction, and cardiosclerosis. The hemodynamic changes caused by atrial fibrillation, causing formation of mural thrombi, is the most important source of emboli [16, 21]. Autopsy studies of heart patients with and without atrial fibrillation showed that the frequency was much higher in the first group [22].

The most frequent cause of emboli among the valve disorders is mitral valve disease, primarily mitral stenosis of rheumatic origin. Thrombi may develop in the subvalvar area, but frequency is greater in the left atrium. Among these patients, two factors appear to be intimately linked with the embolic episode: age and presence of atrial fibrillation [21]. In the past, cardiac valve disease was the main cause of arterial embolism, but advances in the management of these patients have virtually eliminated this as a cause [23–25].

Patients with transmural myocardial infarction are at risk of embolization for 3–4 weeks after the acute event. The majority of these thrombi form in the left ventricle (the region most often involved in myocardial infarctions). Systemic embolization can occur after 5% of after acute myocardial infarction cases [17]. In patients with heart failure, the left atrium or the left ventricle may form thrombi, causing systemic emboli [8].

Another cause of emboli is intracardiac tumors. The tissue of these tumors may dislodge from the heart, causing distal emboli [26].

Acute or subacute bacterial endocarditis can cause arterial emboli, from deposits built up on the valve itself, or by encouraging formation of thrombi. In these cases, the arteries obstructed are generally those of narrower caliber [27].

Nowadays, invasive diagnostic, therapeutic procedures and cardiovascular surgery constitute an important iatrogenic source of peripheral emboli [28, 29]. Thromboembolic complications, including systemic emboli, occur at a rate of 0.7–6% patient-years in thrombosis of mechanical valves [30].

While rare, it is possible for a venous embolus to reach the arterial circulation, causing acute arterial occlusion (paradoxical embolism). In such cases, a thrombus with origin in peripheral veins crosses over to the arterial circulation when the patient has a persistent foramen ovale or intracardiac shunt or there is reversal of the pressure gradients between right and left heart chambers [31].

Cholesterol embolization syndrome (atheroembolism) refers to embolization of the contents of an atherosclerotic plaque (primarily cholesterol crystals) from a proximal large-caliber artery to distal small to medium arteries causing end-organ damage by mechanical plugging and an inflammatory response [32]. Embolization of cholesterol crystals from ulcerated atherosclerotic plaques is well known. Disseminated cholesterol emboli may produce a systemic illness with livedo reticularis of the lower limbs and splinter hemorrhages of the nails [33]. Atheroembolism leads to multifocal ischemic lesions and progressive tissue loss [34] (**Figure 1**). It occurs predominantly in elderly men with a history of atherosclerotic disease and hypertension [35]. Lesions of differing ages were found in individual cases, suggesting that the process of embolism was recurrent [33]. They can occur spontaneously, but are more common after trauma, endovascular procedures, open vascular surgery, thrombolysis, and anticoagulation [36, 37]. Extra-cardiac emboli are very often associated with aortic, iliac, femoral, and popliteal aneurysms. They occur in 5–10% of cases [38].

Tissues' resistance to anoxia is dependent on several factors, which includes metabolic requirements and the effectiveness of collateral circulation [39]. The peripheral nervous system is affected first [40], and therefore loss of sensation is one of the earliest signs of acute leg ischemia [7], the skeletal musculature is affected soon afterwards, and irreversible damage can occur after 6 h of ischemia. The skin, subcutaneous tissue, bone tissues, and cartilage have greater resistance to ischemia [40]. This is why muscle tenderness is one of the end-stage signs of acute leg ischemia [7] **Table 1** shows the lower limb emboli sources.

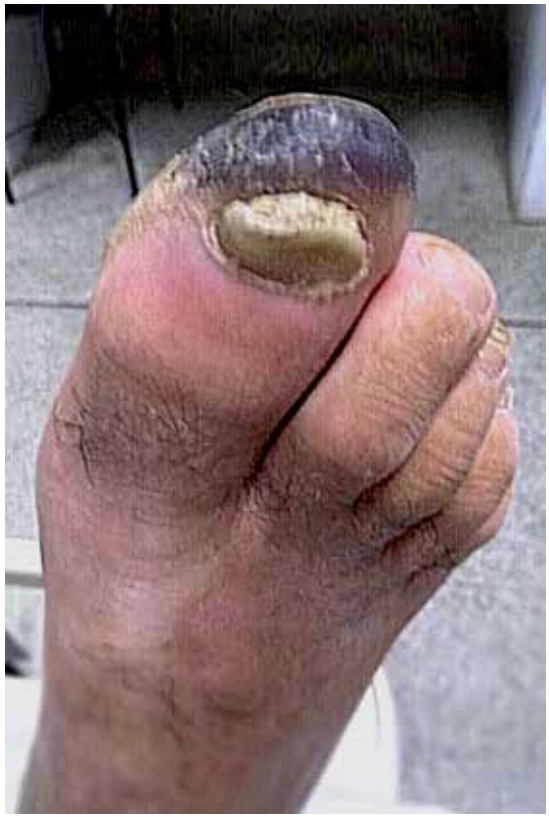

Figure 1.
Atheroembolism.

Cardiac
1. Atrial fibrillation
2. Left ventricular aneurysm
3. Intracardiac shunt
4. Valve disorders
5. Myocardial infarction
6. Heart failure
7. Intracardiac tumors
8. Endocarditis
Extracardiac
1. Aorta-iliac penetrating ulcers
2. Aneurysms of the aorta, iliac, femoral, and popliteal arteries
3. Iatrogenic (invasive diagnostic, therapeutic procedures, cardiovascular surgery, thrombolysis and anticoagulation)
4. Cholesterol embolization syndrome (atheroembolism)
5. Trauma

Table 1.
Lower limb emboli sources.

3. Clinical assessment

The symptoms caused by vascular occlusion depend on the size of the artery occluded and whether collaterals have developed beforehand [7]. The classic description of acute occlusion of a lower limb artery is of acute pain with sudden onset, cyanosis, paresthesia, paralysis, cold, pallor, and absent pulses distal to the site of occlusion (**Figure 2**). The symptoms of paresis, hypoesthesia, or even paralysis are related to ischemic damage to nerve fibers. The segment distal to the occlusion will exhibit pallor of variable extent and intensity, intensifying when the limb is raised. In the majority of cases of acute arterial occlusion, pulses distal of the site of occlusion are absent, but in rare cases they may be present because of collateral circulation. In this patients, onset of pain may be more insidious and pain may be less intense [8]. Therefore, sudden occlusion of a proximal artery without existing collaterals leads to an acute white leg, whereas occlusion of the superficial femoral artery in the presence of well-established collaterals may be asymptomatic [7].

Handheld Doppler examination is also a basic part of the examination. The presence of normal biphasic signals excludes the diagnosis. Pedal arterial signals may be absent or reduced. Soft monophasic signals are associated with patent distal vessels but proximal arterial occlusion. Absent Doppler signals in the ankle arteries is a poor prognostic sign. In severe ischemia, ankle Doppler pressures are impossible to measure. In patients

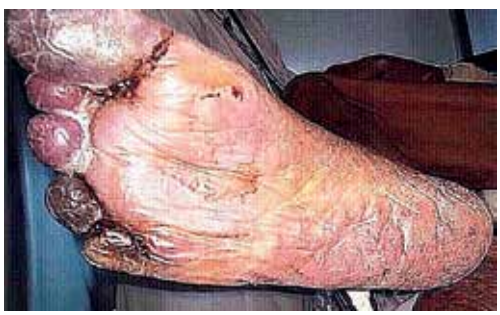

Figure 2.
Clinical assessment of acute arterial embolism of the lower limb.

Category	Description/prognosis	Findings		Doppler signals	
		Sensory loss	**Muscle weakness**	**Arterial**	**Venous**
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
a. Marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Inaudible	Audible
b. Immediately	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve damage inevitables	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

Table 2.
Clinical categories of acute limb ischemia.

with severe ischemia, irreversible muscle necrosis occurs within 6 h if the condition is untreated [7]. The severity of limb ischemia at the time of admission to the hospital seems to be a more important factor in limb salvage than the time interval between embolic episode and operation. Even after long delay, if the limb appears to be viable on examination, the probability exists for a successful operation. This is due to adequate collateral circulation supplying the extremity until the blockage is removed [41].

It is difficult to determine by clinical examination the limits of reversibility of lower limb ischemia. Tissue viability tests should be performed. Rutherford et al. [42], proposed a clinical classification of acute limb ischemia comprising 3 groups in an attempt to establish parameters to define treatment (**Table 2**). Three general classes are recognized:

Class I: Non-threatened extremity; elective revascularization may or may not be necessary.

Class II: Threatened extremity; revascularization is indicated to prevent tissue loss.

Class III: Ischemia has progressed to infarction and salvage of the extremity is not possible.

The most lethal form of acute arterial embolism is emboli of the aortic bifurcation, with symptoms in both lower limbs and in some cases spinal ischemia caused by involvement of lumbar arteries [43].

4. Complementary exams

When time permits, some methods can be used to definitively determine the site and nature of the arterial occlusion. Investigation may be valuable in confirming the clinical diagnosis and planning the treatment for patients with acute ischemia. The modern treatment in a hybrid operating room with access to the full range of surgical and interventional procedures is the best approach. Unfortunately, sometimes there may be no time for investigation [7].

4.1 Ultrasound

The Doppler Ultrasound exam can be employed in cases of acute ischemia to define the level of the arterial occlusion and the patency of other vessels [7]. It can

also provide information that confirms diagnosis and occasionally reveals concurrent venous thrombosis. Detection of distal flow at pressures exceeding 50 mmHg confirms significant collateral circulation, demonstrating that additional time is available to conduct a more thorough evaluation of the case [8]. Portable ultrasound machines may permit rapid, bedside imaging by vascular specialists trained in duplex imaging [7].

4.2 Computed tomographic angiography (CTA)

CTA has become the exam of choice for urgent investigation of acute arterial ischemia [7]. It provides good quality images, offering the possibility of three-dimensional reconstruction, and is of similar quality to angiography [8] (**Figure 3**). A new-generation computed tomography scanners acquire images at very high speed and are available in most emergency suites. The images sometimes require manipulation to produce the best results. These images are particularly good for aortoiliac occlusions but give adequate information to plan treatment of infrainguinal occlusions [7]. It has the disadvantage of using iodine contrast, which restricts use of this examination with patients allergic to iodine or with pre-dialysis chronic stage of renal insufficiency [8]. In these cases, intravenous fluids should be considered for prehydration [7].

4.3 Arteriography

Arteriography was the mainstay of investigation for acute leg ischemia, but it is less accessible than CT angiography in many hospitals without a hybrid operation room [7]. It should be chosen in selected cases with viable extremities, in which it will not delay treatment. Immediately threatened patients should undergo

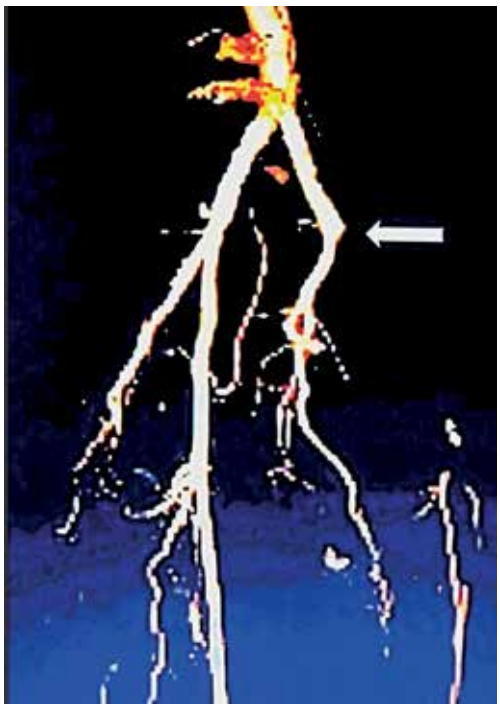

Figure 3.
Angiotomography demonstrating acute arterial embolism in the origin of the left external iliac artery (arrow).

embolectomy at once, conducting arteriography intraoperatively. This examination can reveal the embolic or thrombotic nature of the obstruction in a large number of cases [8]. Brachial puncture can be used in the absence of femoral pulses. The arteriography documents the level of occlusion and sometimes its nature. Sometimes emboli can be seen in several vessels, establishing the diagnosis.

Arteriography may not visualize all the distal vessels in the acute situation, because the lack of collaterals and associated spasm limit visualization. Angiography is the best choice when an endovascular solution to the arterial occlusion is likely, because thrombolysis, percutaneous thrombectomy, angioplasty, or stenting can be performed during the same operative session. It may still be worth exploring distal vessels surgically when contemplating a distal bypass in this situation [7].

There are angiographic signs suggestive of emboli: a filling defect at the level of the occlusion, normal artery wall, poor or absent collateral circulation, and occlusive involvement at bifurcations [8].

4.4 Magnetic resonance angiography (MRI)

It has not yet fully established the point MRI can be used to substitute conventional angiography (which remains the gold standard diagnostic examination) or angiotomography, which offers better results in cases with calcified atherosclerotic plaque [8]. MRI has the advantage to produce an image, without the need of ionizing radiation or nephrotoxic contrast agents [44].

Magnetic resonance angiography with gadolinium is less useful than either CT or ultrasound in the acute limb ischemia. It takes time to acquire images, and is generally inconvenient [7].

4.5 Echocardiography

The echocardiography can be omitted when a cardiac source of embolism appears from the clinical setting [45]. In practical terms, the investigation rarely alters management, because most patients are anticoagulated for life after successful treatment for acute ischemia. There are certainly some conditions that require echocardiography to make a diagnosis, such as valvular disease (including vegetations), septal defect, and cardiac tumor. Problems associated with the routine application of echocardiography include the variability in results between transthoracic and transesophageal techniques, the inability to visualize the left atrial appendage, the fact that failure to visualize the source of an embolus does not rule out its existence, and the test's lack of influence on overall management [46]. A practical view would be that echocardiography is indicated in young patients, those in whom a cardiac diagnosis is suspected, and those in whom the results might affect decisions about long-term anticoagulation [7].

4.6 Laboratory tests

Muscle ischemia is accompanied by a considerable increase in creatine phosphokinase (CPK). The elevation is so marked that for a long time it was considered that CPK level was a determinant of the degree of ischemia and of prognosis of recovery of the ischemic limb after revascularization. The level of leukocytes in circulation may also increase [47]. LDH and SGOT levels are also increased in cases of acute arterial occlusion, because of the ischemic insult to skeletal musculature. Some authors recommend testing levels of LDH, CPK and their respective isozymes in these patients [48, 49].

5. Treatment

Once the initial assessment is complete, a decision should be made about the intervention required and its timing. The threat to the limb escalates with secondary thrombosis of underperfused distal vessels, particularly in patients with emboli. The following options are available: anticoagulation alone, operative intervention, and endovascular intervention via mechanical thrombectomy or thrombolysis [7]. A distinction between subacute (class I) and true limb-threatening ischemia (classes IIa, IIb and III) becomes relevant regarding the urgency of care and risk of limb loss [50].

The choice of intervention depends on the available expertise and the severity of the leg ischemia [1]. There is a suggestion that endovascular first treatment may be more expensive overall [51], but even in modern series, open vascular reconstruction for acute limb ischemia carries a significant risk of major morbidity (20%) or limb loss (22%) [52].

5.1 Auxiliary measures

In patients with there is risk of renal dysfunction, so an intravenous infusion of fluid is appropriate [7]. Other first-aid measures that are beneficial in patients with leg ischemia include the use of oxygen. This has been shown to improve skin perfusion, even in the ischemic limb [53]. A blood sample is indicated. In patients with recurrent thrombosis, a full thrombophilia screen should be performed at this stage [54, 55]. These tests are indicated in patients with a strong family history of arterial and venous thrombosis or those with recurrent disease [56, 57]. Analgesics and sedatives are also employed for pain relief [8].

5.2 Anticoagulation

Heparin should be administered as soon as possible when the acute arterial occlusion has been diagnosed. This drug prevents secondary thrombosis and venous thrombosis that may be present from advancing, both of which are factors that worsen prognosis [58, 59]. Use of anticoagulation alone as a treatment implies that the limb is likely to remain viable or that other therapeutic options are limited, perhaps by age or comorbidity. The anticoagulants made an immediate impact in the morbidity and mortality rates after their introduction [60, 61].

Whereas low-molecular-weight heparin is a valuable therapy for many conditions, the potential for reversal with protamine makes calcium heparin the drug of choice in this situation [7]. The majority of authors recommend intravenous administration of calcium heparin in bolus at a dosage of 5000–10,000 units [58, 59]. In patients in whom definitive treatment is deferred an intravenous heparin infusion (18 U/kg/h) should be prescribed [62].

5.3 Thromboembolectomy

After Fogarty et al. described the embolectomy catheter for the remote removal of a clot via a groin incision in 1963, surgery became the main treatment for acute leg ischemia [63]. The arterial thromboembolectomy is an efficient treatment for acute arterial thromboemboli of lower limbs, especially if a single large artery is involved. Unfortunately, residual thrombus, propagation of thrombi, chronic atherosclerotic disease, and vessel injuries secondary to balloon catheter passage may limit the clinical success rate [64].

While the time elapsed between the embolic episode and effective treatment is an important prognostic factor, experience has shown that good results can still be achieved even with late thromboembolectomy, as long as the limb is viable [11, 65]. The most appropriate access for aortoiliac, femoral, popliteal emboli is the common femoral artery at the femoral triangle (bilaterally for emboli of the aorta) [17] (**Figure 4**). Embolectomy is less likely to be effective for distal occlusions [8].

The benefits of open surgical embolectomy are rapid restoration of blood flow and the ease of the procedure, whereas the risks include a greater physiological stress and concomitant blood loss [50].

5.4 Thrombolysis

Unlike surgical embolectomy, thrombolysis lyses clot in both large and small arteries and arteriolar and capillary beds [66].

Low dose intra-arterial fibrinolytic therapy treatment has its place as an alternative to surgical treatment of acute embolic occlusions in selected cases [67, 68]. The recommendation for intra-arterial thrombolysis is applicable to patients with embolic acute arterial occlusion of less than 14 days duration and with sufficient collateral circulation to maintain limb viability for 12 h [69, 70].

Currently available agents include alteplase (rt-PA), reteplase (rPA), and tenecteplase (TNK). The bolus is delivery of a single concentrated dose of thrombolytic agent throughout the occlusion and then the continuous infusion is initiated. Pulse spray refers to repeated forceful injection of thrombolytic, thus distributing the agent rapidly throughout the thrombus.

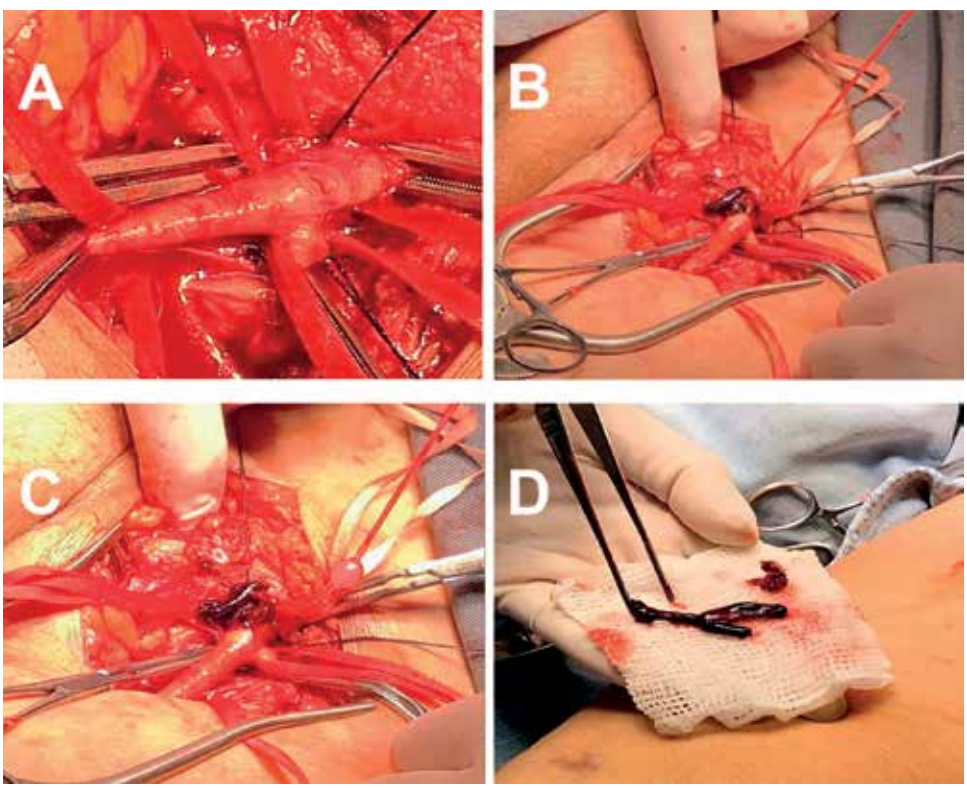

Figure 4.
Embolectomy in lower limb: (A) exposure of the femoral arteries and arteriotomy; (B and C) introduction of the Fogarty catheter for thrombus removal; and (D) thrombi removed from the arterial system.

The commonly used doses today are Alteplase (rt-PA): continuous, 0.5–1.0 mg/kg/h (40 mg maximum); bolus, 2–5 mg bolus, then continuous infusion; pulse spray, 0.5 mg/mL at 0.2 mL every 30–60 seconds, Reteplase (rPA): continuous, 0.25–0.5 U/h (20 units maximum); bolus, 2–5 U bolus, then continuous infusion and Tenecteplase (TNK): continuous, 0.125–0.25 mg/h; bolus, 1–5 mg, then continuous infusion (20).

Streptokinase, the first-generation agent, is still used in some centers. This drug is used intra-arterially, by continuous infusion through a multiperforated catheter, positioned immediately before the obstruction, with release of the thrombolytic inside the thrombus, activating plasminogen bound to it [71]. This technique made it possible to use streptokinase at much lower doses, reducing the risk of hemorrhage, while maintaining its thrombolytic power. The dose used is 5000 UI/h, controlling coagulation status every 12 h by fibrinogen assay, TP, and TTPA, attempting not to allow fibrinogen to fall below 100 mg%. Good results are achieved using this technique [72–74], although there are hemorrhagic complications in up to 20% of cases [59]. The infusion is then maintained at a dosage of 1 mg/h and the patient is kept anticoagulated with unfractionated heparin on a continuous infusion pump [8]. Heparin can be infused intravenously or intra-arterially through the sheath. A bolus at the time of thrombolysis initiation is not recommended. An infusion rate to raise PTT to only 1.25–1.5 of control is recommended. Most practitioners use between 200 and 500 U/h [20].

Some prospective and randomized studies compared direct thrombolysis with surgical revascularization in cases of acute arterial occlusion and the two approaches were not different for limb salvage or mortality, but fibrinolysis was associated with a higher risk of hemorrhagic events [66, 75–77].

5.4.1 Contraindications to thrombolytic therapy

Many patients with acute limb ischemia are not candidates for thrombolysis because of excessive major bleeding risks. All major and minor contraindications should be viewed in the context of the clinical circumstance. The increased risk of bleeding complications may be assumed if the alternative is likely limb loss or death [20]. **Table 3** lists thrombolytics contraindications [78].

When using thrombolytics, arteriography should be performed every 6 h, or in the event of changes to the patient's clinical. Fibrinogen assay also should be performed every 6 h. If the results of these tests are undesirable, fibrinolytic agent should be suspended [8].

The criteria for successful thrombolysis are radiological evidence of lysis with arterial recanalization at least as far as the next major collateral, an increase in the ankle brachial index greater than or equal to 0.2, limb salvage at 30 days without recourse to reconstructive surgery at the level at which lysis was performed and no clinical evidence or rethrombosis within the first 30 days [79].

5.5 Percutaneous aspiration thrombectomy

The treatment of the arterial embolism of the lower limb has evolved significantly, especially regarding the development of endovascular devices.

Percutaneous aspiration thrombectomy is another resource that offers and is an alternative to surgical treatment and can be combined with angioplasty or fibrinolytic therapy [80, 81]. These materials generally employ simple mechanisms for aspiration or destruction of the thrombus [82].

Promising results were obtained for percutaneous mechanical thrombectomy, employing a range of different equipment [81, 83–86]. The trend is that endovascular treatment significantly evolves, with the development of new and less invasive of these devices.

Absolute
1. Established cerebrovascular event (including transient ischemic attacks within last 2 months)
2. Active bleeding diathesis
3. Recent gastrointestinal bleeding (<10 days)
4. Neurosurgery (intracranial, spinal) within last 3 months
5. Intracranial trauma within last 3 months
Relative major
1. Cardiopulmonary resuscitation within last 10 days
2. Major nonvascular surgery or trauma within last 10 days
3. Uncontrolled hypertension: >180 mmHg systolic or >110 mmHg diastolic
4. Puncture of noncompressible vessel
5. Intracranial tumor
6. Recent eye surgery
Minor
1. Hepatic failure, particularly those with coagulopathy
2. Bacterial endocarditis
3. Pregnancy
4. Diabetic hemorrhagic retinopathy

Table 3.
Thrombolysis contraindications.

6. Postoperative anticoagulation

Postoperative anticoagulation is recommended long term and, sometimes, even indefinitely, in cases of atrial fibrillation and arterial emboli in which the source of origin is not identified or is not controlled [11]. One study demonstrated 31% recurrence of emboli in patients not taking anticoagulants during the postoperative period vs. 9% among those taking anticoagulants [16].

New drugs are currently used for postoperative anticoagulation, mainly factor Xa inhibitors. There are evidences to justify its use, in order to prevent recurrent episodes.

7. Postoperative complications

High operative mortality among patients suffering from acute ischemia is a well-established observation. Both serious cardiac disease and reperfusion injury contribute to mortality [87].

Mortality from acute arterial occlusion are reported from 7 to 37% and the amputation rate in patients with embolism 10–30% [88, 89].

Acute myocardial infarction and arrhythmia are responsible for the majority of deaths and, despite advances in technology and clinical support, mortality among acute arterial occlusion patients remains high [8], particularly among the elderly [90]. One study demonstrated that New York Heart Association (NYHA) classification was the most important predictor for survival (class 3–4 had a 3.35 times higher death rate than class 1–2) [91]. Advanced age, recent myocardial infarction and proximal occlusions are also associated with a high mortality rate after arterial thromboembolectomy [92].

7.1 Compartment syndrome

After limb revascularization (particularly if ischemia is intense and prolonged) compartment syndrome may occur. This is due to edema increasing the pressure

in muscle compartments situated between inelastic fascia and bones, which can compromise tissue perfusion. It may be caused by a chain of events secondary to ischemia-reperfusion, including with release of thromboxane A2 [8]. The ischemia-reperfusion phenomenon plays an important role in the pathogenesis of compartment syndrome due. Ischemia-reperfusion increases compartment volume by causing muscle tissue injury, which leads to increased microvascular permeability, with efflux of plasma proteins and progressive interstitial edema [93]. With reperfusion, oxygen radical generation exacerbates microvascular permeability and resulting interstitial edema [94].

For diagnosis, some authors describe tissue pressures exceeding 30–45 mmHg [95, 96]. However, there are also authors who recommend diagnosis based on clinical criteria alone (spontaneous pain, pain on flexion or passive extension of the foot, tense edema, hypoperfusion, missing pulse, paresthesia, anesthesia, paresis, or paralysis) [8]. Risk factors for compartment syndrome after acute arterial ischemia includes prolonged ischemia time, young age, insufficient arterial collaterals, acute time course for arterial occlusion, hypotension and poor back-bleeding from the distal arterial tree at embolectomy [94].

Once a diagnosis of compartment syndrome has been made, fasciotomy should be conducted promptly, since it releases muscle compression, reestablishes capillary blood flow, and restores the caliber of arteries e veins. In general, this procedure is associated with low morbidity. The staged fasciotomy technique is generally sufficient to decompress the anterior and posterior compartments. If this does not provide sufficient relief of compression, 4-compartment fasciotomy should be performed via a wide incision. Incisions can be sutured after 1–2 weeks or heal by secondary intention [8].

7.2 Ischemia: reperfusion injury

This primarily occurs after ischemia of large muscle masses, which can develop local and systemic metabolic abnormalities after arterial desobstruction and reperfusion of ischemic tissues [97]. One study demonstrated a 7.5% incidence of this syndrome in patients with acute arterial occlusion, with 4.7% mortality [98].

Serious metabolic abnormalities can develop with ischemia of the lower limb muscle mass [99]. Ischemia compromises the integrity of the cell membrane and cause cellular dysfunction [100–102]. The reperfusion can exacerbate it, making the damage irreversible [103].

Tissue hypoxia results in movement of neutrophils and macrophages into the interstitium through the action of hypoxia adaptive pathways [104–106]. Activated neutrophils subsequently release molecular mediators, which contribute to the production of adenosine on the vascular endothelial surface, a protective factor that restores endothelial integrity [107, 108]. Activated leukocytes also have significant pro-inflammatory consequences. Neutrophils release factors that increase endothelial permeability and cytoskeletal rearrangement [109].

During ischemia, the supply of oxygen to cells is reduced, decreasing aerobic metabolism and, consequently, reducing the energy available for maintenance of cellular metabolism [110]. In consequence of the reduced energy supply, the sodium-potassium-ATPase protein is affected and the sodium and potassium pump fails, resulting in cellular edema and ion flow disorders [111].

Oxygen free radicals are produced by molecular oxygen reintroduced into the ischemic tissue during reperfusion [102]. They can cause cell injury by reacting with polysaturated fatty acids, leading to peroxidation of lipid components in the membrane [112], which can rupture cell integrity [102] and attract leukocytes to the ischemic tissues. Reperfusion of ischemic tissue can have effects that are highly damaging to the

function of distant organs [113]. Data are emerging regarding the important role of the tumor necrosis factor-α (TNF-α), released from activated macrophages [114].

Serious pulmonary injuries, such as low oxygen tension, pulmonary edema, pulmonary hypertension and inflammatory response, can be caused by the activity of mediators such as free oxygen radicals, thromboxane, leukotrienes and neutrophils [115, 116].

Serum potassium levels can vary after revascularization. Hyperkalemia is a consequence of myocytolysis and, in combination with acidosis, can lead to myocardial depression, hypotension, arrhythmia, and cardiac arrest. Renal dysfunction may occur, depending on the degree of metabolic acidosis, muscle injury, myoglobinuria and hypovolemia [117, 118].

Adjuvants measures can be useful to attenuate or avoid additional damage to cells during the reperfusion period. These measures include hypothermia, controlled reperfusion, and hemodilution [119]. In some cases, it can be useful to drain the effluent blood from the limb, immediately after revascularization, with the objective of removing toxic products that have built up during the period of ischemia [18]. Free radical scavengers still need to be further evaluated for their efficacy for reducing post-reperfusion cellular damage [120]. There is evidence that antioxidant vitamins and calcium channel blockers could be useful for attenuating ischemia-reperfusion cell damage [121]. Preventative measures for ischemia-reperfusion syndrome are alkalinization, osmotic diuresis and correction of hyperkalemia. Red blood cells can be washed, resuspended, and reinfused [122, 123], primarily in cases with muscle rigidity [122].

8. Future avenues/developments

Advances in this area are evident. For many years, there was no specific treatment for lower limb embolism. The most serious cases were treated only with analgesia and amputation. The Fogarty catheter revolutionized the prognosis of these patients. Now, ever-greater advances are made, and even less invasive treatments gain space.

The tendency is that endovascular treatment, including fibrinolysis and percutaneous aspiration, evolves more and more, with the development of new and less invasive devices, and will probably be considered the treatment of choice for embolic occlusion of the lower limb.

9. Conclusion

Acute limb ischemia of the lower extremity is a potentially devastating condition that requires urgent and definitive management. The two principal etiologies of acute ischemia of the lower limbs are arterial embolism and in situ thrombosis of an atherosclerotic artery.

Despite major advances in the contemporary management of peripheral arterial occlusive disease, acute ischemia of the lower limb is still characterized by an important morbidity, limb threat, mortality, and continues to pose a challenge to the vascular surgeon.

Atrial fibrillation, left ventricular aneurysm, penetrating ulcers or aneurysms of the aorta and common iliac arteries are the common sources of emboli. The presence of occlusion can be determined noninvasively with the use of duplex Doppler ultrasonography. If time permits, Arteriography, Computed Tomographic Angiography and Magnetic Resonance Angiography can also be employed.

Embolectomy is the standard procedure for acute leg ischemia, mainly in patients with a strong clinical suspicion of an embolus, but alternative techniques, such as catheter-directed thrombolysis or percutaneous aspiration thrombolectomy, expand the role of radiologic percutaneous therapy of the acutely ischemic limb.

The worse consequences of acute limb ischemia are prolonged hospitalization, major limb amputation, and death, so prevention strategies should be aimed to avoid the episode.

Conflict of interest

The author has no conflicts of interest to disclose.

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References

[1] Creager MA, Kaufman JA, Conte MS. Clinical practice. Acute limb ischemia. The New England Journal of Medicine. 2012;**366**:2198-2206. DOI: 10.1056/NEJMcp1006054

[2] Van DH, Boesmans E, Defraigne JO. Acute limb ischemia. Revue Médicale de Liège. 2018;**73**:304-311

[3] Dormandy J, Heeck L, Vig S. Acute limb ischemia. Seminars in Vascular Surgery. 1999;**12**:148-153

[4] Kronlage M, Printz I, Vogel B, Blessing E, Muller OJ, Katus HA, et al. A comparative study on endovascular treatment of (sub)acute critical limb ischemia: Mechanical thrombectomy vs thrombolysis. Drug Design, Development and Therapy. 2017;**11**: 1233-1241. DOI: 10.2147/DDDT.S131503

[5] Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). Journal of Vascular Surgery. 2007;**45**(Suppl S):S5-S67. DOI: 10.1016/j.jvs.2006.12.037

[6] Karnabatidis D, Spiliopoulos S, Tsetis D, Siablis D. Quality improvement guidelines for percutaneous catheter-directed intra-arterial thrombolysis and mechanical thrombectomy for acute lower-limb ischemia. Cardiovascular and Interventional Radiology. 2011;**34**:1123-1136. DOI: 10.1007/s00270-011-0258-z

[7] Sidawy AN, Perler BA. Rutherford's Vascular Surgery and Endovascular Therapy. 9th ed. New York: Elsevier; 2018. p. 2832

[8] Maffei FHA, Yoshida WB, Rollo HA, Moura R, Sobreira ML, Giannini M, et al. Doenças Vasculares Periféricas. 5th ed. Vol. 2015. Rio de Janeiro: Guanabara Koogan. p. 2368

[9] Blaisdell FW. The pathophysiology of skeletal muscle ischemia and the reperfusion syndrome: A review. Cardiovascular Surgery. 2002;**10**:620-630. DOI: 10.1177/096721090201000620

[10] Andersen LV, Lip GY, Lindholt JS, Frost L. Upper limb arterial thromboembolism: A systematic review on incidence, risk factors, and prognosis, including a meta-analysis of risk-modifying drugs. Journal of Thrombosis and Haemostasis. 2013;**11**:836-844. DOI: 10.1111/jth.12181

[11] Elliott JP Jr, Hageman JH, Szilagyi E, Ramakrishnan V, Bravo JJ, Smith RF. Arterial embolization: Problems of source, multiplicity, recurrence, and delayed treatment. Surgery. 1980;**88**:833-845

[12] Hight DW, Tilney N, Couch NP. Changing clinical trends in patients with peripheral arterial emboli. Surgery. 1976;**79**:172-176

[13] MacGowan WA, Mooneeram R. A review of 174 patients with arterial embolism. The British Journal of Surgery. 1973;**60**:894-898. DOI: 10.1002/bjs.1800601115

[14] Dale WA. Differential management of acute peripheral arterial ischemia. Journal of Vascular Surgery. 1984;**1**:269-278. DOI: 10.1016/0741-5214(84)90058-2

[15] Fogarty TJ, Daily PO, Shumway NE, Krippaehne W. Experience with balloon catheter technic for arterial embolectomy. American Journal of Surgery. 1971;**122**:231-237. DOI: 10.1016/0002-9610(71)90323-0

[16] Green RM, DeWeese JA, Rob CG. Arterial embolectomy before and after the Fogarty catheter. Surgery. 1975;**77**:24-33

[17] Panetta T, Thompson JE, Talkington CM, Garrett WV, Smith BL. Arterial embolectomy: A 34-year experience with 400 cases. The Surgical Clinics of North America. 1986;**66**:339-353. DOI: 10.1016/S0039-6109(16)43886-7

[18] Chin AK, Fogarty TJ. Management of arterial emboli. Gleanings from 20 years of experience. Postgraduate Medicine. 1987;**81**:271-276. DOI: 10.1080/00325481.1987.11699833

[19] Connett MC, Murray DH Jr, Wenneker WW. Peripheral arterial emboli. American Journal of Surgery. 1984;**148**:14-19. DOI: 10.1016/0002-9610(84)90283-6

[20] Harry L, Morrison I. Catheter-directed thrombolysis for acute limb ischemia. Seminars in Interventional Radiology. 2006;**23**:258-269. DOI: 10.1055/s-2006-948765

[21] Colman RW, Hirsh J, Marder VJ, et al. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. Philadelphia: Lippincott Williams & Wilkins; 2006. 1827 p

[22] Hinton RC, Kistler JP, Fallon JT, Friedlich AL, Fisher CM. Influence of etiology of atrial fibrillation on incidence of systemic embolism. The American Journal of Cardiology. 1977;**40**:509-513. DOI: 10.1016/0002-9149(77)90064-9

[23] Haimovici H. Peripheral arterial embolism: A study of 330 unselected cases of embolism of the extremities. Angiology. 1950;**1**:20-45. DOI: 10.1177/000331975000100103

[24] Abbott WM, Maloney RD, McCabe CC, Lee CE, Wirthlin LS. Arterial embolism: A 44 year perspective. American Journal of Surgery. 1982;**143**:460-464. DOI: 10.1016/0002-9610(82)90196-9

[25] Tawes RL Jr, Harris EJ, Brown WH, Shoor PM, Zimmerman JJ, Sydorak GR, et al. Arterial thromboembolism. A 20-year perspective. Archives of Surgery. 1985;**120**:595-599. DOI: 10.1001/archsurg.1985.01390290073012

[26] Lyaker MR, Tulman DB, Dimitrova GT, Pin RH, Papadimos TJ. Arterial embolism. International journal of critical illness and injury science. 2013;**3**:77-87. DOI: 10.4103/2229-5151.109429

[27] Kitts D, Bongard FS, Klein SR. Septic embolism complicating infective endocarditis. Journal of Vascular Surgery. 1991;**14**: 480-485 ; discussion 485-487. DOI: 10.1016/0741-5214(91)90241-L

[28] Kalliafas S, Albertini JN, Macierewicz J, Yusuf SW, Whitaker SC, Davidson I, et al. Stent-graft migration after endovascular repair of abdominal aortic aneurysm. Journal of Endovascular Therapy. 2002;**9**:743-747. DOI: 10.1177/152660280200900605

[29] Bui JT, West DL, Pinto C, Gramling-Babb P, Owens CA. Right ventricular migration and endovascular removal of an inferior vena cava filter. Journal of Vascular and Interventional Radiology. 2008;**19**: 141-144. DOI: 10.1016/j.jvir.2007.09.014

[30] Tourmousoglou C, Karkos C, Fidanis T, Theofilogiannakos EK, Hytiroglou P, Pitsis A. An unusual case of arterial embolism in an adolescent with a mitral valve repair with a ring. The Annals of Thoracic Surgery. 2017;**104**:e315-e317. DOI: 10.1016/j.athoracsur.2017.04.051

[31] Ward R, Jones D, Haponik EF. Paradoxical embolism. An underrecognized problem. Chest. 1995;**108**:549-558. DOI: 10.1378/chest.108.2.549

[32] Saric M, Kronzon I. Cholesterol embolization syndrome. Current Opinion in Cardiology. 2011;**26**:472-479. DOI: 10.1097/HCO.0b013e32834b7fdd

[33] Cross SS. How common is cholesterol embolism? Journal of Clinical Pathology. 1991;**44**:859-861. DOI: 10.1136/jcp.44.10.859

[34] Mayo RR, Swartz RD. Redefining the incidence of clinically detectable atheroembolism. The American Journal of Medicine. 1996;**100**:524-529. DOI: 10.1016/S0002-9343(95)00059-3

[35] Moolenaar W, Lamers CB. Cholesterol crystal embolization in the Netherlands. Archives of Internal Medicine. 1996;**156**:653-657. DOI: 10.1001/archinte.1996.00440060081009

[36] Scolari F, Tardanico R, Zani R, Pola A, Viola BF, Movilli E, et al. Cholesterol crystal embolism: A recognizable cause of renal disease. American Journal of Kidney Diseases. 2000;**36**:1089-1109. DOI: 10.1053/ajkd.2000.19809

[37] Higginson A, Alaeddin F, Fishwick G, Bolia A. "Push and park": An alternative strategy for management of embolic complication during balloon angioplasty. European Journal of Vascular and Endovascular Surgery. 2001;**21**:279-282. DOI: 10.1053/ejvs.2001.1324

[38] Karnabatidis D, Katsanos K, Kagadis GC, Ravazoula P, Diamantopoulos A, Nikiforidis GC, et al. Distal embolism during percutaneous revascularization of infra-aortic arterial occlusive disease: An underestimated phenomenon. Journal of Endovascular Therapy. 2006;**13**:269-280. DOI: 10.1583/05-1771.1

[39] Perry MO. Compartment syndromes and reperfusion injury. The Surgical Clinics of North America. 1988;**68**:853-864. DOI: 1016/S0039-6109(16)44590-1

[40] Blebea J, Kerr JC, Franco CD, Padberg FT Jr, Hobson RW 2nd. Technetium 99m pyrophosphate quantitation of skeletal muscle ischemia and reperfusion injury. Journal of Vascular Surgery. 1988;**8**:117-124. DOI: 10.1016/0741-5214(88)90397-7

[41] Silvers LW, Royster TS, Mulcare RJ. Peripheral arterial emboli and factors in their recurrence rate. Annals of Surgery. 1980;**192**:232-236

[42] Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: Revised version. Journal of Vascular Surgery. 1997;**26**:517-538. DOI: 10.1016/S0741-5214(97)70045-4

[43] Busuttil RW, Keehn G, Milliken J, Paredero VM, Baker JD, Machleder HI, et al. Aortic saddle embolus. A twenty-year experience. Annals of Surgery. 1983;**197**:698-706

[44] Hartung MP, Grist TM, Francois CJ. Magnetic resonance angiography: Current status and future directions. Journal of Cardiovascular Magnetic Resonance. 2011;**13**:19. DOI: 10.1186/1532-429X-13-19

[45] Egeblad H, Andersen K, Hartiala J, Lindgren A, Marttila R, Petersen P, et al. Role of echocardiography in systemic arterial embolism. A review with recommendations. Scandinavian Cardiovascular Journal. 1998;**32**:323-342. DOI: 10.1080/14017439850139780

[46] Gossage JA, Ali T, Chambers J, Burnand KG. Peripheral arterial embolism: Prevalence, outcome, and the role of echocardiography in management. Vascular and Endovascular Surgery. 2006;**40**:280-286. DOI: 10.1177/1538574406291820

[47] Kvilekval KH, Yunis JP, Mason RA, Giron F. After the blue toe: Prognosis of noncardiac arterial embolization in the lower extremities. Journal of Vascular Surgery. 1993;**17**:328-334; discussion 334-325. DOI: 10.1016/0741-5214(93)90418-L

[48] Nevins MA, Saran M, Bright M, Lyon LJ. Pitfalls in interpreting serum creatine phosphokinase activity. Journal of the American Medical Association. 1973;**224**:1382-1387. DOI: 10.1001/jama.1973.03220240032008

[49] Russell SM, Bleiweiss S, Brownlow K, Elevitch FR. Ischemic rhabdomyolysis and creatine phosphokinase isoenzymes: A diagnostic pitfall. Journal of the American Medical Association. 1976;**235**:632-633. DOI: 10.1001/jama.1976.03260320040023

[50] Eliason JL, Wainess RM, Proctor MC, Dimick JB, Cowan JA Jr, Upchurch GR Jr, et al. A national and single institutional experience in the contemporary treatment of acute lower extremity ischemia. Annals of Surgery. 2003;**238**:382-389; discussion 389-390. DOI: 10.1097/01.sla.0000086663.49670.d1

[51] Lurie F, Vaidya V, Comerota AJ. Clinical outcomes and cost-effectiveness of initial treatment strategies for nonembolic acute limb ischemia in real-life clinical settings. Journal of Vascular Surgery. 2015;**61**:138-146. DOI: 10.1016/j.jvs.2014.07.086

[52] Baril DT, Patel VI, Judelson DR, Goodney PP, McPhee JT, Hevelone ND, et al. Outcomes of lower extremity bypass performed for acute limb ischemia. Journal of Vascular Surgery. 2013;**58**:949-956. DOI: 10.1016/j.jvs.2013.04.036

[53] Berridge DC, Hopkinson BR, Makin GS. Acute lower limb arterial ischaemia: A role for continuous oxygen inhalation. The British Journal of Surgery. 1989;**76**:1021-1023. DOI: 10.1002/bjs.1800761011

[54] Linnemann B, Schindewolf M, Zgouras D, Erbe M, Jarosch-Preusche M, Lindhoff-Last E. Are patients with thrombophilia and previous venous thromboembolism at higher risk to arterial thrombosis? Thrombosis Research. 2008;**121**:743-750. DOI: 10.1016/j.thromres.2007.07.014

[55] Lijfering WM, Coppens M, van de Poel MH, Middeldorp S, Hamulyak K, Bank I, et al. The risk of venous and arterial thrombosis in hyperhomocysteinaemia is low and mainly depends on concomitant thrombophilic defects. Thrombosis and Haemostasis. 2007;**98**:457-463. DOI: 10.1160/TH07-02-0138

[56] Deitcher SR, Carman TL, Sheikh MA, Gomes M. Hypercoagulable syndromes: Evaluation and management strategies for acute limb ischemia. Seminars in Vascular Surgery. 2001;**14**:74-85. DOI: 10.1053/svas.2001.23156

[57] de Moerloose P, Boehlen F. Inherited thrombophilia in arterial disease: A selective review. Seminars in Hematology. 2007;**44**:106-113. DOI: 10.1053/j.seminhematol.2007.01.008

[58] Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: The seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest. 2004;**126**:401S-428S. DOI: 10.1378/chest.126.3_suppl.401S

[59] Hirsh J, Guyatt G, Albers GW, Harrington R, Schunemann HJ. Antithrombotic and thrombolytic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest. 2008;**133**:110S-112S. DOI: 10.1378/chest.08-0652

[60] Murray GDW. Heparin in thrombosis and embolism. The British Journal of Surgery. 1940;**27**:567-598. DOI: 10.1002/bjs.18002710718

[61] Blaisdell FW, Steele M, Allen RE. Management of acute lower

extremity arterial ischemia due to embolism and thrombosis. Surgery. 1978;**84**:822-834

[62] Ram B, George R. Nontraumatic acute limb ischemia–presentation, evaluation, and management. Indian Journal of Vascular and Endovascular Surgery. 2017;**4**:192

[63] Fogarty TJ, Cranley JJ, Krause RJ, Strasser ES, Hafner CD. A method for extraction of arterial emboli and thrombi. Surgery, Gynecology & Obstetrics. 1963;**116**:241-244

[64] de Donato G, Setacci F, Sirignano P, Galzerano G, Massaroni R, Setacci C. The combination of surgical embolectomy and endovascular techniques may improve outcomes of patients with acute lower limb ischemia. Journal of Vascular Surgery. 2014;**59**: 729-736. DOI: 10.1016/j.jvs.2013.09.016

[65] Levin BH, Giordano JM. Delayed arterial embolectomy. Surgery, Gynecology & Obstetrics. 1982;**155**:549-551

[66] van den Berg JC. Thrombolysis for acute arterial occlusion. Journal of Vascular Surgery. 2010;**52**:512-515. DOI: 10.1016/j.jvs.2010.01.080

[67] Earnshaw JJ. Thrombolytic therapy in the management of acute limb ischaemia. The British Journal of Surgery. 1991;**78**:261-269. DOI: 10.1002/bjs.1800780304

[68] Hess H. Thrombolytic therapy in peripheral vascular disease. The British Journal of Surgery. 1990;**77**:1083-1084. DOI: 10.1002/bjs.1800771003

[69] Lawrence PF, Goodman GR. Thrombolytic therapy. The Surgical Clinics of North America. 1992;**72**:899-918

[70] Hanover TM, Kalbaugh CA, Gray BH, Langan EM 3rd, Taylor SM, Androes MP, et al. Safety and efficacy of reteplase for the treatment of acute arterial occlusion: Complexity of underlying lesion predicts outcome. Annals of Vascular Surgery. 2005;**19**:817-822. DOI: 10.1007/s10016-005-8047-2

[71] Rush DS, Gewertz BL, Lu CT, Neely SM, Ball DG, Beasley M, et al. Selective infusion of streptokinase for arterial thrombosis. Surgery. 1983;**93**:828-833

[72] Dardik H, Sussman BC, Kahn M, Greweldinger J, Adler J, Mendes D, et al. Lysis of arterial clot by intravenous or intra-arterial administration of streptokinase. Surgery, Gynecology & Obstetrics. 1984;**158**:137-140

[73] Berni GA, Bandyk DF, Zierler RE, Thiele BL, Strandness DE Jr. Streptokinase treatment of acute arterial occlusion. Annals of Surgery. 1983;**198**:185-191

[74] Slany J, Enzenhofer V, Karnik R. Local thrombolysis in arterial occlusive disease. Angiology. 1984;**35**:231-237. DOI: 10.1177/000331978403500405

[75] Ouriel K, Shortell CK, Green RM, DeWeese JA. Differential mechanisms of failure of autogenous and non-autogenous bypass conduits: An assessment following successful graft thrombolysis. Cardiovascular Surgery. 1995;**3**:469-473. DOI: 10.1177/096721099500300505

[76] Ouriel K, Veith FJ, Sasahara AA. A comparison of recombinant urokinase with vascular surgery as initial treatment for acute arterial occlusion of the legs. Thrombolysis or peripheral arterial surgery (TOPAS) investigators. The New England Journal of Medicine. 1998;**338**:1105-1111. DOI: 10.1056/NEJM199804163381603

[77] Comerota AJ, Weaver FA, Hosking JD, Froehlich J, Folander H, Sussman B,

et al. Results of a prospective, randomized trial of surgery versus thrombolysis for occluded lower extremity bypass grafts. American Journal of Surgery. 1996;**172**: 105-112. DOI: 10.1016/S0002-9610(96)00129-8

[78] Working Party on Thrombolysis in the Management of Limb I. Thrombolysis in the management of lower limb peripheral arterial occlusion–a consensus document. Journal of Vascular and Interventional Radiology. 2003;**14**:S337-S349. DOI: 10.1016/S1051-0443(07)61244-5

[79] Yusuf SW, Whitaker SC, Gregson RH, Wenham PW, Hopkinson BR, Makin GS. Prospective randomised comparative study of pulse spray and conventional local thrombolysis. European Journal of Vascular and Endovascular Surgery. 1995;**10**:136-141. DOI: 10.1016/S1078-5884(05)80104-2

[80] Huettl EA, Soulen MC. Thrombolysis of lower extremity embolic occlusions: A study of the results of the STAR registry. Radiology. 1995;**197**:141-145. DOI: 10.1148/radiology.197.1.7568812

[81] Schleder S, Diekmann M, Manke C, Heiss P. Percutaneous aspiration thrombectomy for the treatment of arterial thromboembolic occlusions following percutaneous transluminal angioplasty. Cardiovascular and Interventional Radiology. 2015;**38**: 60-64. DOI: 10.1007/s00270-014-0857-6

[82] Horsch AD, van Oostayen J, Zeebregts CJ, Reijnen MM. The Rotarex(R) and Aspirex(R) mechanical thrombectomy devices. Surgical Technology International. 2009;**18**:185-192

[83] Starck EE, McDermott JC, Crummy AB, Turnipseed WD, Acher CW, Burgess JH. Percutaneous aspiration thromboembolectomy. Radiology. 1985;**156**:61-66. DOI: 10.1148/radiology.156.1.3159042

[84] Reekers JA, Kromhout JG, Spithoven HG, Jacobs MJ, Mali WM, Schultz-Kool LJ. Arterial thrombosis below the inguinal ligament: Percutaneous treatment with a thrombosuction catheter. Radiology. 1996;**198**:49-53. DOI: 10.1148/radiology.198.1.8539405

[85] Rilinger N, Gorich J, Scharrer-Pamler R, Vogel J, Tomczak R, Kramer S, et al. Short-term results with use of the Amplatz thrombectomy device in the treatment of acute lower limb occlusions. Journal of Vascular and Interventional Radiology. 1997;**8**:343-348. DOI: 10.1016/S1051-0443(97)70569-4

[86] Wagner HJ, Starck EE. Acute embolic occlusions of the infrainguinal arteries: Percutaneous aspiration embolectomy in 102 patients. Radiology. 1992;**182**:403-407. DOI: 10.1148/radiology.182.2.1732957

[87] Aune S, Trippestad A. Operative mortality and long-term survival of patients operated on for acute lower limb ischaemia. European Journal of Vascular and Endovascular Surgery. 1998;**15**:143-146. DOI: 10.1016/S1078-5884(98)80135-4

[88] Kuukasjarvi P, Salenius JP. Perioperative outcome of acute lower limb ischaemia on the basis of the national vascular registry. The Finnvasc study group. European Journal of Vascular Surgery. 1994;**8**:578-583. DOI: 10.1016/S0950-821X(05)80594-8

[89] Neuzil DF, Edwards WH Jr, Mulherin JL, Martin RS 3rd, Bonau R, Eskind SJ, et al. Limb ischemia: Surgical therapy in acute arterial occlusion. The American Surgeon. 1997;**63**:270-274

[90] Braithwaite BD, Davies B, Birch PA, Heather BP, Earnshaw JJ. Management of acute leg ischaemia

in the elderly. The British Journal of Surgery. 1998;**85**:217-220. DOI: 10.1046/j.1365-2168.1998.00577.x

[91] Dregelid EB, Stangeland LB, Eide GE, Trippestad A. Patient survival and limb prognosis after arterial embolectomy. European Journal of Vascular Surgery. 1987;**1**:263-271. DOI: 10.1016/S0950-821X(87)80078-6

[92] Baxter-Smith D, Ashton F, Slaney G. Peripheral arterial embolism. A 20 year review. The Journal of Cardiovascular Surgery. 1988;**29**:453-457

[93] Sexton WL, Korthuis RJ, Laughlin MH. Ischemia-reperfusion injury in isolated rat hindquarters. Journal of Applied Physiology (Bethesda, MD: 1985). 1990;**68**:387-392. DOI: 10.1152/jappl.1990.68.1.387

[94] Papalambros EL, Panayiotopoulos YP, Bastounis E, Zavos G, Balas P. Prophylactic fasciotomy of the legs following acute arterial occlusion procedures. International Angiology. 1989;**8**:120-124

[95] Mubarak SJ, Owen CA, Hargens AR, Garetto LP, Akeson WH. Acute compartment syndromes: Diagnosis and treatment with the aid of the wick catheter. The Journal of Bone and Joint Surgery. American Volume. 1978;**60**:1091-1095

[96] Rollins DL, Bernhard VM, Towne JB. Fasciotomy: An appraisal of controversial issues. Archives of Surgery. 1981;**116**:1474-1481. DOI: 10.1001/archsurg.1981.01380230088014

[97] Haimovici H. Arterial embolism with acute massive ischemic myopathy and myoglobinuria: Evaluation of a hitherto unreported syndrome with report of two cases. Surgery. 1960;**47**:739-747

[98] Haimovici H. Proceedings: Myopathic-nephrotic-metabolic syndrome associated with massive acute arterial occlusions. The Journal of Cardiovascular Surgery. 1973;**14**:589-600

[99] Eliason JL, Wakefield TW. Metabolic consequences of acute limb ischemia and their clinical implications. Seminars in Vascular Surgery. 2009;**22**:29-33. DOI: 10.1053/j.semvascsurg.2009.01.001

[100] Braunwald E, Kloner RA. Myocardial reperfusion: A double-edged sword? The Journal of Clinical Investigation. 1985;**76**:1713-1719. DOI: 10.1172/JCI112160

[101] Bulkley GB. Pathophysiology of free radical-mediated reperfusion injury. Journal of Vascular Surgery. 1987;**5**:512-517. DOI: 10.1016/0741-5214(87)90085-1

[102] Perry MO. Postischemic cell membrane dysfunction. Journal of Vascular Surgery. 1990;**11**:179-180. DOI: 10.1016/0741-5214(90)90343-9

[103] Walker PM. Pathophysiology of acute arterial occlusion. Canadian Journal of Surgery. 1986;**29**:340-342

[104] Bradbury AW, Brittenden J, McBride K, Ruckley CV. Mesenteric ischaemia: A multidisciplinary approach. The British Journal of Surgery. 1995;**82**:1446-1459. DOI: 10.1002/bjs.1800821105

[105] Brezis M, Rosen S. Hypoxia of the renal medulla—Its implications for disease. The New England Journal of Medicine. 1995;**332**:647-655. DOI: 10.1056/NEJM199503093321006

[106] Cagin YF, Atayan Y, Sahin N, Parlakpinar H, Polat A, Vardi N, et al. Beneficial effects of dexpanthenol on mesenteric ischemia and reperfusion injury in experimental rat model. Free Radical Research. 2016;**50**:354-365. DOI: 10.3109/10715762.2015.1126834

[107] Cannistra M, Ruggiero M, Zullo A, Gallelli G, Serafini S, Maria M, et al. Hepatic ischemia reperfusion injury: A systematic review of literature and the role of current drugs and biomarkers. International Journal of Surgery. 2016;**33**(Suppl 1):S57-S70. DOI: 10.1016/j.ijsu.2016.05.050

[108] Chen J, Vemuri C, Palekar RU, Gaut JP, Goette M, Hu L, et al. Antithrombin nanoparticles improve kidney reperfusion and protect kidney function after ischemia-reperfusion injury. American Journal of Physiology. Renal Physiology. 2015;**308**:F765-F773. DOI: 10.1152/ajprenal.00457.2014

[109] Collard CD, Vakeva A, Morrissey MA, Agah A, Rollins SA, Reenstra WR, et al. Complement activation after oxidative stress: Role of the lectin complement pathway. The American Journal of Pathology. 2000;**156**:1549-1556. DOI: 10.1016/S0002-9440(10)65026-2

[110] Haljamae H, Enger E. Human skeletal muscle energy metabolism during and after complete tourniquet ischemia. Annals of Surgery. 1975;**182**:9-14

[111] Hayes PG, Liauw S, Smith A, Romaschin AD, Walker PM. Exogenous magnesium chloride-adenosine triphosphate administration during reperfusion reduces the extent of necrosis in previously ischemic skeletal muscle. Journal of Vascular Surgery. 1990;**11**:441-447. DOI: 10.1016/0741-5214(90)90245-6

[112] Del Maestro RF. An approach to free radicals in medicine and biology. Acta Physiologica Scandinavica. Supplementum. 1980;**492**:153-168

[113] Huk I, Nanobashvili J, Neumayer C, Punz A, Mueller M, Afkhampour K, et al. L-arginine treatment alters the kinetics of nitric oxide and superoxide release and reduces ischemia/reperfusion injury in skeletal muscle. Circulation. 1997;**96**:667-675

[114] Wajant H, Pfizenmaier K, Scheurich P. Tumor necrosis factor signaling. Cell Death and Differentiation. 2003;**10**:45-65. DOI: 10.1038/sj.cdd.4401189

[115] Anner H, Kaufman RP Jr, Valeri CR, Shepro D, Hechtman HB. Reperfusion of ischemic lower limbs increases pulmonary microvascular permeability. The Journal of Trauma. 1988;**28**:607-610

[116] Back M. Leukotriene signaling in atherosclerosis and ischemia. Cardiovascular Drugs and Therapy. 2009;**23**:41-48. DOI: 10.1007/s10557-008-6140-9

[117] Karam H, Bruneval P, Clozel JP, Loffler BM, Bariety J, Clozel M. Role of endothelin in acute renal failure due to rhabdomyolysis in rats. The Journal of Pharmacology and Experimental Therapeutics. 1995;**274**:481-486

[118] Zager RA, Burkhart KM, Conrad DS, Gmur DJ. Iron, heme oxygenase, and glutathione: Effects on myohemoglobinuric proximal tubular injury. Kidney International. 1995;**48**:1624-1634. DOI: 10.1038/ki.1995.457

[119] Beyersdorf F, Schlensak C. Controlled reperfusion after acute and persistent limb ischemia. Seminars in Vascular Surgery. 2009;**22**:52-57. DOI: 10.1053/j.semvascsurg.2009.01.005

[120] Ricci MA, Graham AM, Corbisiero R, Baffour R, Mohamed F, Symes JF. Are free radical scavengers beneficial in the treatment of compartment syndrome after acute arterial ischemia? Journal of Vascular Surgery. 1989;**9**:244-250. DOI: 10.1016/0741-5214(89)90043-8

[121] Ozcan AV, Sacar M, Aybek H, Bir F, Demir S, Onem G, et al. The effects

of iloprost and vitamin C on kidney as a remote organ after ischemia/reperfusion of lower extremities. The Journal of Surgical Research. 2007;**140**:20-26. DOI: 10.1016/j.jss.2006.04.031

[122] Celoria G, Zarfos K, Berman J. Effects of acute lower limb ischemia on femoral venous efflux. Angiology. 1990;**41**:439-444. DOI: 10.1177/000331979004100604

[123] Perry MO, Fantini G. Ischemia: Profile of an enemy. Reperfusion injury of skeletal muscle. Journal of Vascular Surgery. 1987;**6**:231-234. DOI: 10.1016/0741-5214(87)90033-4

Chapter 6

Thrombophilia and Pregnancy: Diagnosis and Management

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Abstract

Thromboembolic disease during pregnancy is a significant cause of maternal morbidity and mortality involving venous or arterial thrombosis and possible clinical manifestations like clinical symptoms of antiphospholipid antibody syndrome and hyperhomocysteinemia. For diminishing the prevalence of thromboembolic disease, the early identification of pregnant women with various risk factors for thrombosis without clinical symptoms is of great importance. However, the optimal management for asymptomatic pregnant women who have inherited thrombophilia is uncertain and recognized only due to pregnancy complications such as recurrent pregnancy loss and preeclampsia. The clinical approach to thromboembolism is the same in pregnant women with or without thrombophilia. Based on family history, clinical symptoms should begin with simple reliable inexpensive laboratory tests like prothrombin time and activated thromboplastin time to test the status. Early diagnosis and appropriate use of thromboprophylaxis lead to increasing better maternal and perinatal outcomes. Conclusively, it is important to recognize these patients in order to prevent all pregnancy complications.

Keywords: thromboembolic diseases, pregnancy, diagnostic criteria, complications, treatment

1. Introduction

It is well known that thromboembolic disease is an important cause of maternal morbidity and mortality [1, 2]. Moreover, pregnancy is a period of increased coagulation [1, 2]. The above underlines the need to assess thrombotic risk at all stages of pregnancy [3, 4]. To detect pregnancies with an increased risk of thromboembolic disease requires an individual, family history of thromboembolic events, obesity, or surgery [3, 4]. In order to reduce the incidence of this condition, it is necessary to identify women with multiple risk factors for thrombosis during pregnancy [5, 6]. In women with an individual or family history of proven thromboembolic disease,

examination for thrombophilia should be performed at the beginning of pregnancy [5, 6].

The term *thrombophilia* is used to describe a blood coagulation disorder and includes a series of conditions with increased risk of blood clot formation in vessels. It may be congenital or acquired, and all the symptoms depend on the location as well as the extent of thrombosis [7, 8]. Thrombophilia was first introduced by Egeberg in 1965 and until now expresses any disorder related to anticoagulant mechanism causing increase tendency for venous thromboembolism, deep vein thrombosis, or pulmonary embolism [7, 8].

Congenital thrombophilia: It is used for inborn and more often hereditary abnormalities. On the contrary, *acquired thrombophilia* refers to all cases that present later in life.

Inherited thrombophilia: In this case, patients present earlier the first thromboembolic episode in comparison with general population. In addition, many clinical types of hereditary thrombophilia are associated with pregnancy complications such as *recurrent miscarriage*, preeclampsia, endometrial growth retardation, and HELLP syndrome [9–14].

Completely inherited thrombophilia causes:

- Antithrombin III deficiency.
- Protein C deficiency.
- Protein S deficiency.
- Mutation in factor V.
- Prothrombin gene mutation.

Partially inherited thrombophilia causes:

- High levels factor VIIIc.
- Mild hyperhomocysteinemia.

2. Inherited thrombophilia causes

Antithrombin and C protein are natural coagulation inhibitors, so any deficiency of them predispose for thrombosis. Leiden mutation of factor V is the most common thrombophilic abnormality making anticoagulant protein secreted enable to bind to factor V. Prothrombin G20210A gene mutation is also frequent, causing high levels of inactive prothrombin [15]. Increased factor VIII levels above the 75th position are also a strong risk factor for thromboembolic disease, as well as mild hyperhomocysteinemia (**Table 1)** [13].

Thrombophilia is a group of disorders that stimulate blood clotting. Patients with thrombophilia form clots very easily, either because they produce in excess certain proteins called coagulation factors or because they produce less anticoagulants [15–18].

Most thrombophilic patients are unware for their disease because they do not demonstrate symptoms. However, some will develop a thrombus at some place. Usually clots present in the lower limbs, deep vein thrombosis, causing edema, redness, and dysphoria. These clots can lead into lethal events if they move and

	General population	Thromboembolic history (%)
Antithrombin, C-protein and protein S deficiency	1%	7
Factor V Leiden	Caucasian: 4–7% Non-Caucasian: 0–1%	21
Prothrombin G20210A	Caucasian: 2–3% Non-Caucasian: 0–1%	6
High levels factor VIIIc	11%	25
Mild hypehomocysteinemia	55	10

Table 1.
Appearance of Inherited thrombophilia.

travel via blood circulation to vital organs (venous thromboembolism). When the clots block vessels in the lungs, brain, or heart, it can lead to embolism, stroke, or heart attack. A thrombophilia can also increase the risk of coronary artery disease. Clots are more frequent in patients with additional risk factors like immobility or undergoing surgery. Pregnancy is a status when the signs of thrombophilia are very common [15–18].

In general, women with thrombophilia do not have more pregnancies with complications, but late pregnancy loss in the first or later in the second trimester, placental abruption, and incomplete fetal development are the most frequent. Also, thrombophilia may be clots implicated in preeclampsia. These problems are believed to arise due to thrombus formation in the placenta, a phenomenon that leads to changes in the placenta and a reduced blood flow to the fetus. Pregnant patients with thrombophilia have a higher risk of developing thromboembolic disease than pregnant women without thrombophilia. Generally, pregnancy is a period of increased risk for thromboembolic disease even in women without thrombophilia. This is due to the changes accompanying normal pregnancy involving blood clotting and limiting the loss of blood during childbirth. In the USA, pulmonary embolism is the first cause of maternal death [7, 19–21].

3. Risk factors for thromboembolic disease associated with pregnancy

During pregnancy, normal changes occur in the coagulation system. According to the literature, an increase in coagulation factors Vc, VIIIc, Xc, and von

Hereditary disorders	Acquired disorders
Prothrombin III deficiency	Antiphospholipid syndrome
C & S protein deficiency	Paroxysmal nocturnal hemoglobinuria
Factor V Leiden Hyperhomocysteinemia	Hyperhomocysteinemia Myeloproliferative disorders
Prothrombin G20210A	Cancer
Dysfibrinogenemia	Inflammatory bowel disease
Factor VII, XII & plasminogen deficiency	Nephrotic syndrome
High levels of factor VII, IX, XI, tPA, PAI	Cardiac insufficiency

Table 2.
Risk factors leading to thrombosis disorders.

Willebrand factor antigen and reduction in total and free S protein have been observed. In addition, coagulation activation markers are increased particularly in the third trimester of pregnancy. There is no significant change in plasma levels of protein C or antithrombin III throughout pregnancy. The increase in platelet-derived inhibitor of typ. 2 plasminogen activation (PAI-2), which is produced in increased amounts during pregnancy, partly contributes to the attenuation of fibrinolytic activity. These physiological changes during pregnancy develop a relative thrombotic tendency. Moreover, during pregnancy, cesarean section, previous thromboembolic event, high BMI, multiple pregnancies, infections, preeclampsia, immobility, and maternal age are additional risk factors for venous thromboembolic events **(Table 2)** [13, 22–24].

4. Pregnancy complications

Inherited thrombophilia is present almost in the half of the cases of pregnancy-associated venous thromboembolic events (VTE). Homozygous women with Leiden or prothrombin gene mutation have double risk for recurrent miscarriage in the first trimester [22].

It is well known that during pregnancy, levels of coagulation proteins like protein S, protein C, and antithrombin III are decreased, but deficiencies in these factors can easily lead to hypercoagulation. On the other hand, women with antithrombin deficiency and hyperhomocysteinemia may lead to higher risk of placental abruption. Finally, there is no evident correlation between high level VIIIc and preeclampsia, IUGR (intrauterine growth retardation), and HELLP syndrome [22–24].

5. Follow-up in women with inherited thrombophilia in pregnancy

Every woman with vein thrombosis or pulmonary embolism history is thoroughly investigated by laboratory tests, but in the case of acute thromboembolic event during pregnancy, the treatment is not affected by the laboratory results. Therefore, diagnostic tests must be taken before anticoagulant regimen or 1 month after. The results must be evaluated keeping in mind that protein's S levels are normally decreased in pregnancy. Furthermore, almost 40% of women with no mutation of factor V Leiden are presented with resistance of protein C. Moreover, decreased protein S, C, and antithrombin are widely observed if another disease like hepatopathy or nephritic syndrome coexists in pregnancy [25–29].

Low molecular weight heparin (LMWH) does not go through the placenta and is safe for the fetus, as well as decreases the risk of bleeding. In addition, LMWH is more stable and causes less platelet activation because of less binding of platelet factor 4. The risk of thrombocytopenia is decreased [25].

6. Mechanisms of thrombosis in congenital thrombophilia

The mechanism of thrombosis in most cases of congenital thrombophilia is the inability to inactivate thrombin or in the failure to control the production of thrombin. Natural anticoagulants, such as antithrombin, retain the fluidity of the blood. Antithrombin binds to heparin sulfate or endothelial cells and inactivates thrombin, factor XIa, factor IXa, and factor Xa. Another anticoagulant, protein C, controls the production of thrombin. When thrombin is bound to thrombomodulin

in the blood vessels of the small blood vessels, thrombin is inactivated, and protein C is activated [30–33].

In large vessels, connection of protein C to its receptor increases the activation of protein C by thrombin. In turn activated protein C inactivates factors Va and VIII in the presence of free S protein and phospholipids to prevent the production of thrombin. Free S protein has anticoagulant effects: it prevents the prothrombinase complex (agents Xa, Va, and phospholipids) that converts prothrombin to thrombin and the supportive complex (factors IXa, VIIIa, and phospholipids) that converts factor X to Xa. The reduction in antithrombin activity prevents the inactivation of thrombin, and the reduced energy of protein C or protein S minimizes control of thrombin production. The aforementioned mechanisms increase the vulnerability to venous thrombosis [30–33].

Mutations in the involved genes endanger the human organism. Mutations in the factor V gene or prothrombin modify the thrombin production control. Replacement of Arg 506Gln factor V Leiden leads to a deceleration of proteolytic Va inactivation, which results in increased production of thrombin. The mutant factor V also decreases the action of the cofactor in the inactivation of VIIIa by activated protein C [30–33].

7. Classification

Most types of thrombophilia are inherited, but there are some forms that appear later in life. The two most common forms are associated with mutations in factor V Leiden and prothrombin. Both of these forms are inherited in an autosomal dominant way. Another common form, mild hyperhomocysteinemia (MTHFR methylenetetrahydrofolate reductase), is inherited in an autosomal recessive status. More rare forms include deficiencies of antithrombin III and C and S proteins [34–39].

Antiphospholipid syndrome (APS) is a thrombophilia that is not inherited but can later occur in life. In this syndrome, the body develops antibody to phospholipid-bound proteins. These antibodies are suspected of damaging the vessels, leading to clot formation. Therefore, the APS is considered as an autoimmune disease [40–44].

In the question which women should be tested for thrombophilia, the answer is that all pregnant women with a history of thrombus should be controlled according to the American College of Obstetricians and Gynecologists. Doctors may suggest screening for women with a family history of thrombi, pulmonary embolism, or stroke that occurred before the age of 60 years or a history of complications during pregnancy (including two or more miscarriages, a fatal embryo, preeclampsia, placental abruption, or poor embryo development) [40–44].

Thrombophilia is considered to be a major predictor of thrombosis. Acquired thrombophilia includes the lack of endogenous anticoagulants, protein C and S antithrombin, genetic mutations in procoagulants such as FV-Leiden (FVL), prothrombin G2021OA, and the methylenetetrahydrofolate reductase or methylenetetrahydrofolate methylene (MTHFR) gene [40–44].

Another group of thrombophilic diseases combine hereditary and acquired characteristics such as factor VIIIc elevated, hyperhomocysteinemia, and acquired activated C protein. Hereditary thrombophilia is due to autosomal mutations of specific genes, which are inherited by one or both parents and are implicated in a significant rate of miscarriage [44–49].

The major of these genes are:

7.1.1 Factor V Leiden

1. Coagulation factor V and mutation (FV-Leiden-G1691A)

This mutation is one of the most common and most important genetic factors of propensity for congenital thrombophilia. In the Greek population, it represents at 6–10%, while homozygous individuals are rarely detected.

In fact, heterozygous women have a 2–3 times increased risk of miscarriages, as well as other complications such as preeclampsia and delayed fetal development. Detection of a further mutation of A4044G in the same gene, although in itself, is a mild thrombophilic agent, however, in combination with the FV-Leiden mutation, increases the risk of thrombosis and, moreover, miscarriages [44, 45].

Prothrombin G20210A

2. Prothrombin or coagulation factor II (FII) or F2

The detection of G2021OA mutation in the F2 gene is the second most common form of thrombophilia, after factor V Leiden, and in our country reaches 4%. The risk of vascular disease or auto-elimination in heterozygotes increases about three-fold compared to the general population and homozygotes 20 times [46–49].

3. Gene of hyperhomocysteinemia: methylenetetrahydrofolate reductase or methylene tetrahydrofolate (MTHFR).

Two important mutations, C677T and A1298C, have been implicated in the deficiency of this enzyme, which leads to elevated levels of plasma cytotoxic homocysteine. The C677T mutation is an important predictor of severe arterial and venous deep vein thrombosis and infertility in men and women.

The risk of thrombosis is greater in subjects coexisting with the M77F mutation of the V77-Leiden mutant [46–49].

7.1.2 Protein C deficiency

This deficiency is inherited by the autosomal dominant formula, presenting over 160 different mutations. Protein C deficiency is associated with familial thrombosis with phenotypic variation. The heterozygous disorder is associated with adverse events during pregnancy, such as deep vein thrombosis, preeclampsia, endometrial growth retardation, and abortions. In cases of homozygosity, they have been associated with a neonatal purple thunderbolt. Heterozygotes have an increased risk of deep vein thrombosis by 8–10 times [46–49].

7.1.3 Protein S deficiency, antithrombin deficiency, and dysfibrinogenemia

This disorder is inherited by the autosomal dominant way. It is heterogeneous, numbering over 330 different mutations. The mechanism by which thrombosis is caused by abnormal fibrinogen production is not fully elucidated. Dysfibrinogenemia is sometimes manifested by a bleeding disposition or by a thrombotic and hemorrhagic image [39–49].

With the recognition of factor V Leiden and the G20210A mutation of the prothrombin gene, the proportion of patients with venous thrombosis has increased, in which the diagnosis of hereditary thrombophilia can be established. The predominant areas of thrombosis during pregnancy are the luteal veins and veins of the foot [39–49].

The term thrombophilia includes inherited or acquired lack of antithrombin, as well as secondary syndromes characterized by either reduced levels of coagulation inhibiting agents or elevated levels of coagulation factors. The age of the first thromboembolic event is 10 years less for the general population [39–49].

Several clinical forms of hereditary thrombophilia are associated with pregnancy complications such as abortions, preeclampsia, lethal newborns, endometrial growth retardation, and HELLP syndrome.

Universal hereditary thrombophilia is due to antithrombin deficiency, protein C deficiency, protein S deficiency, factor V mutation, and mutation of the prothrombin gene 20210A. Increased factor VIIIc levels and mild hyperhomocysteinemia are linked to multifactorial or partial inherited thrombophilia.

The natural inhibitors of coagulation are antithrombin and C and S proteins. Factor V Leiden mutation is the most frequent thrombophilic disorder. The prothrombin mutation 2010A generates higher levels of inactive prothrombin; elevated factor VIII levels above the 75th percentile are a risk factor for thromboembolic disease and mild hyperhomocysteinemia [39–49]. There is a double incidence of first trimester abortions in prothrombin or V Leiden factor mutants. For the other types, there is limited bibliographic data.

Cardinally, the relationship between hereditary thrombophilia and the incidence of pregnancy loss appears to influence all stages of pregnancy. Concerning the other complications, preeclampsia, lethargy, placental detachment, and delayed intrauterine growth seem to be more associated with factor V mutation. The lack of protein S or C appears to be also associated more with preeclampsia and unexplained lethal neonates. Hyperhomocysteinemia and prothrombin mutation appear to be most associated with placental ablation. Finally, there seems to be no relationship between elevated factor VIIIc levels and preeclampsia, IUGR, and HELLP syndrome.

Laboratory findings include increased levels of factor VIII and fibrinogen, decreased levels of protein S, resistance to activated protein C, decreased fibrinolysis and Leiden factor V mutation, and G20210A antithrombin mutation. Monitoring of pregnant women with hereditary thrombophilia involves the implementation of a complete laboratory investigation. Laboratory testing is a common practice in women with a history of venous thrombosis or pulmonary embolism [39–49].

However, in the case of an acute thromboembolic event in pregnancy, the control is of limited value because it does not significantly affect the clinical response. Therefore, this laboratory investigation should be done either before anticoagulation treatment or 1 month after its discontinuation [39–49].

Laboratory findings should be interpreted with caution because levels of protein S show a normal decrease in pregnancy and resistance to protein C occurs in 40% of pregnancies without factor V Leiden disorder.

Also the coexistence of some other disease (liver disease, nephrotic syndrome) can cause a decrease in C and S protein levels and antithrombin, respectively [39–49].

In contrast to pregnancy, the genotypes for factor V Leiden and prothrombin G20210A can be safely interpreted. Treatment include thromboprophylaxis with low molecular weight heparin (enoxaparin 0.5-1mg/kg/12 hours or dalteparin 50-100 IU/kg/12 hours) in combination with compression stockings. It is more recommended for antithrombin and symptomatic patients [39–49]. Enoxaparin 40 mg or dalteparin 5000 IU should be given daily for 4–6 weeks. Low MB heparin does not penetrate the placenta, and so there is no risk of embryo or hemorrhage. Also in relation to classical heparin, it affects more favorably the anticholate (antithrombotic) anti-Xa versus anti-IIa (anticoagulant) effect resulting in a reduced risk of bleeding. It also exhibits stable and predictable pharmacological activity and causes less platelet activation due to less binding to platelet factor 4, reducing the risk of thrombocytopenia.

Antiphospholipid syndrome (APS) is common in patients with autoimmune diseases. Antiphospholipid antibodies are associated to these diseases (lupus, scleroderma, etc.) [39–49]. In pregnancy, the mechanism of increasing venous thrombosis in the antiphospholipid syndrome is not well known. The presence of lupus anticoagulant is severe and can cause fetal bradycardia around the 25th week of pregnancy and atrioventricular blockages [39–49].

APS diagnostic criteria include:

1. Vascular thrombosis.
2. Gestational complications.
3. Anticardiolipin antibodies.
4. Diluted Russell viper venom time (dRVVT).
5. Clot-based LAC (which detects the in vitro inhibitory activity of aPL antibodies).
6. aPTT with silica as an activator (silica clotting time).
7. Kaolin clotting time (KCT).
8. Dilute prothrombin time (dPT).
9. Ecarin clotting time (ECT).
10. Textarin clotting time.

International Society on Thrombosis and Hemostasis (ISTH) and other guidelines recommend dRVVT as the first choice to confirm the diagnosis of APS and an aPTT with low phospholipids and silica activator as second choice [50–54]. Vascular thrombosis is the diagnosis of one or more clinical episodes of arterial, venous, or capillary thrombosis in any tissue or organ.

Diagnosis of the antiphospholipid syndrome needs the existence of at least one clinical and laboratory criteria [50–54]. Anticardiolipin or lupus anticoagulants are found in two or more measurements of moderate or high levels of IgG-IgM antibodies for a period of at least 6 weeks. In case of history with one or more unexplained endometrial deaths of normal morphological embryos from the 10th week of pregnancy or one or more premature births at week 34 and before or three unexplained consecutive abortions before the 10th week of pregnancy, anticardiolipin should be tested. As a consequence miscarriage is defined as the loss of three or more pregnancies before the 20th week of pregnancy [50–54].

The mechanism in the abovementioned syndrome is not precisely specified. Potential microtubule mechanisms are included, including autoantibody failure to implant or develop embryo-fetal circulation. The abortions in the first trimester may be due to insufficient trophoblast development and failure to produce effective embryo-fetal circulation. They may also be due to thrombosis in the uterine-pulmonary circulation due to inadequate binding to factor V trophoblast [50–54]. In older gestational age, endometrial deaths are attributable to massive thrombosis in the placenta, while mechanisms associated with other complications (preeclampsia) are unknown.

Despite the lack of large cross-references, the treatment pathway includes corticosteroids, aspirin, heparin, and coumarin [55–59]. In addition, the treatments proposed are associated with a high risk for the mother and the fetus. Treatment should only be used when the risk of complications is considered to be greater and after a thorough discussion of pregnancy. Predictive poor outcome factors are the title of anticardiolipin antibodies and the obstetrical history. Corticosteroids have been extensively used in the past, but this practice was to a great extent abandoned after the publication of Laskin et al. which revealed increased maternal morbidity without sufficient evidence of improvement in perinatal outcome. Adoption is only recommended in cases where the syndrome is complicated by clinically manifest thrombocytopenia or lupus erythematosus. In these cases, a systematic check for the possibility of diabetes mellitus or gestational hypertension is necessary [55–59]. Aspirin inhibits the formation of thromboxane and reduces the risk of thrombosis due to platelet aggregation. It can be used during pregnancy because it usually does not cause complications in the mother and the fetus. The use of low-dose aspirin can be continued until delivery without significantly increasing the risk of epidural hemorrhage in the application of epidural anesthesia. Regarding the efficacy of the above treatment as monotherapy, there are currently no satisfactory conclusions according to two recent studies [55–59]. Low molecular weight heparin is considered to be safer than classical.

Regarding the duration of treatment, others recommend prophylactic administration until completion of the 37th week, suggesting then induction of labor and other administration until the birth occurs automatically with concomitant administration of vitamin K antagonists [55–59]. Over-the-counter gamma globulin is no longer recommended because there is no evidence of a clear improvement in perinatal outcomes.

Coumarins are not particularly administered in the first and third trimesters as potential teratogens and cause colonic disorders in the embryos due to easy passage through the placenta and because they are associated with greater maternal morbidity. Administration of these is indicated only in minimal cases of contraindication for the administration of heparin or aspirin [55–59]. The complications of antithrombotic therapy in pregnancy include embryo-phytopathy (nasal hypoplasia, stiff epiphyses), CNS abnormalities (Dandy-Walker syndrome, visual atrophy), embryonic hemorrhage, bleeding events, skin allergies, thrombocytopenia, and osteoporosis [60–64].

Hyperhomocysteinemia is characterized by elevated fasting plasma homocysteine (> 100 μmol/L in severe cases). The mild to moderate form has less elevated fasting plasma homocysteine levels (>15–100 μmol/L). It causes homocystinuria, cataracts, skeletal abnormalities, early angiopathy, thromboembolic events, and mental retardation [60–64]. Characterized as a risk factor for thromboembolic disease. Homocysteine levels are higher in males and increase with age. On the contrary, pregnancy and estrogen decrease levels, due to genetic factors (lack of β-synthase of cystathionine, or 5,10-methylenetetrahydrofolate reductase) [60–64]. There are also environmental factors that affect homocysteine levels (decreased folic acid uptake and methionine intake, smoking, increased coffee intake, decreased renal function, hypothyroidism, and certain drugs such as methotrexate, steroids, cyclosporin, etc.). Homocysteine levels decrease during pregnancy because of increased renal infiltration and hemodilution. Moreover, the fetus increases the uptake of homocysteine. The high levels are linked to neural tube damages, placental thrombosis, preeclampsia, and placental abruption. Also, the rate of early abortion is increased [60–64].

The proposed mechanisms include vascular endothelial dysfunction, cell apoptosis due to reduced nitrogen oxide bioactivity, decrease in antioxidant regulation,

changes in platelet activity, elimination of prostacyclin biosynthesis pathway, decrease in antithrombin activity, inhibition of protein C activation, and inhibition of binding to the endothelium of the tissue plasminogen receptor [65–69].

Treatment includes substitution with vitamin B12 (0.5 mg/day) and folate (0.5–5 mg/day). It is a low-risk treatment that reduces homocysteine levels in most cases. Research clinical protocols have shown that B6 administration did not have significant results [65–69]. However, according to recent trials, vitamin administration did not contribute significantly to the reduction of complications. On the other hand, the administration of folic acid at a dose of 5 mg/day reduced the incidence of preeclampsia and prematurity and contributed to the increase in birth weight. The latest results have not been adequately proved [65–69].

Consequently, hyperhomocysteinemia is a common and easily treatable cause of arterial and venous thrombosis. The various treatments should be administered with caution because there is a risk of increased thrombus incidence. It is worth mentioning other acquired thrombophilia such as increased levels of coagulation factors VIII, IX, and sometimes factor XI. The levels of these factors increase in pregnancy with the main purpose of reducing the loss of blood in childbirth. The levels of these factors increase in pregnancy with the main purpose of reducing the loss of blood in labor [65–69].

In Europe, the annual incidence of deep vein thrombosis is about 124/100.000 and 60–70/100.00 for pulmonary embolism (PE). Especially in Greece PE is affecting 1800 persons each year. In bibliography there are guidelines for prevention by the National Drug Organization and the Greek Society of Orthopedics and Trauma but not for diagnosis of thrombosis [65–69].

The DVT diagnosis is based on Wells score for DVT, levels of d-dimmers, venous duplex or triplex ultrasonography and in rare cases on MRA. Wells score, EEG, chest X-ray, arterial gas blood values, D-dimers, CTPA, V/Q scan, PA, and MRA are used for PE diagnosis. D-dimer test has high sensitivity (80–85%), 99% negative predictive value, and 30% positive predictive value. The normal value of 500 μg/L depends on the age. In accord with ACP guidelines, the D-dimer value arises from the type: age x 10 μg/L. In general, d-dimers value used in patients with Wells score <2 or in patients with intermediate or with low pretest probability of PE who do not meet all Pulmonary Embolism Rule-Out Criteria (ACP guidelines) [65–69].

In patients whose PE is unlike, D-dimer assay plays important role in diagnosis, as well as diagnosis is excluded in values under 500 ng/mL. On the other hand, spiral-CT pulmonary angiogram (CTPA) is a tool diagnosing PE in patients who are in high risk.

In pregnancy, Wells test is not validated, but negative D-dimers are quite useful. Serial, proximal ultrasonography and iliac vein ultrasound or abdominal magnetic resonance venography can be also used. The treatment of acute VTE and PE includes UFH, LMWH, fondaparinux, DOACS (direct oral anticoagulants), and antivitamin K. Body weight-based LMWH or fixed dose of fondaparinux (7.5 mg) is initially used, and after 1 or 2 days VKA (acenocoumarol) is added. An alternative scheme includes rivaroxaban or apixaban from day 1 or dabigatran after 5–10 days of heparin administration. Anti-Xa monitoring is indicated in pregnant women, in patients with renal disease, and in underweight patients [65–69].

DOACS monitoring is not in routine. It is useful in the case of hemorrhage, before surgery, and before and after use of antidote. The available DOACS in Greece are dabigatran (DTI) and rivaroxaban, apixaban, and edoxaban (anti-Xa). Among acenocoumarol and dabigatran or rivaroxaban, the prices have extremely high difference [65–69].

Warfarin is still preferred in cases of mechanical valves, rheumatic mitral valve disease, advanced renal failure, cancer patients (if LMWH is not used), and high-risk thrombophilia. Quantitative monitoring of DOACS is not a routine but can be

applied in special cases such as elderly, low body weight, and low renal function. It is well known that normal aPTT indicates that high dabigatran levels are not present. Rivaroxaban prolongs PT in a linear and concentration-dependent way. Idarucizumab is dabigatran antidote that can be used in life-threatening bleeding. Hemodialysis can also reduce the plasma levels by 60% within 2 hours. Andexanet is the anti-Xa antidote but is not yet approved [65–69].

Temporary inferior vena cava filters are an alternative method for fibrinolysis when patients with PE or DVT cannot have anticoagulation treatment or in patients with recurrent proximal DVT or PE, despite adequate anticoagulation treatment.

HIT II diagnosis is based on 4Ts score. Stop heparin and start alternative anticoagulation such as anti-Xa or DTIs are the first step of management. When PLTs >150.000/μL VKAs can be added. The treatment duration varies from 4 weeks up to 3 months in VTE [65–69].

After the first DVT episode, the decision for long-term anticoagulation is based on risk of thrombosis versus the risk of a major bleeding. At least a 3-month duration therapy is recommended except in the cases of active cancer, recurrent VTE, and high risk of thrombophilia as APS. Three different treatment phases in VTE and PE can be described: the initial, just for the first few days; the short term, up to 3–6 months; and the long term, beyond the first 6 months. HER DOO algorithm has been applied as a rule for clinical decisions. As a result, hyperpigmentation, edema or redness, D-dimers >250 μg/L, obesity (BMI > 30 kg/m^2), and older age (>65yo) have major importance for the patient profile. Gender also plays important role, as men have 2.2-fold higher risk of recurrent disease than women.

DOACS are the first choice for the long-term therapy. Next choices are VKA and LMWH. In contrast, LMWH for 6 months is the first choice for cancer patients.

Regarding aspirin role, INSPIRE trial shows that after the first unprovoked VTE, it can reduce the overall risk for VTE recurrence more than one third, without significant increase of bleeding risk [65–69].

The most common mutation associated with thrombophilia in Greece is MTHFR C677T (35%), whereas FV-Leiden and prothrombin G20210A have an incidence of about 2%.

Candidates for thrombophilia testing are people with family history of venous thrombosis, onset in young people (<45yo), thrombosis in unusual sites, people with secondary VTE in pregnancy, HTR or oral contraception intake, and patients with recurrent VTE. Although, the clinical practice is quite different and investigation of thrombophilia is much more frequent.

Protein C activity, free PS activity, antithrombin activity assay, activated protein C resistance, prothrombin G20210A mutation assay, anticardiolipin antibodies, and lupus anticoagulant testing are among diagnostic panel for thrombophilia.

It is important to keep in mind that 3–5% of patients with an unprovoked DVT and no obvious sign of cancer has an occult cancer.

In cases of acquired thrombophilia, diagnosis of antiphospholipid syndrome is based on revised Sapporo criteria. Primary prophylaxis is not recommended in APS. First-line treatment is VKAs and in pregnancy cases LMWH and aspirin.

According to recent studies, DOACS have no big importance in inherited thrombophilia treatment.

8. Thrombophilia test: is it necessary and when?

Thrombophilia test aims to identify individuals at increased risk of VTE or relapse or complications in pregnancy associated with hereditary or acquired thrombophilia.

The type of laboratory investigation is generally influenced by:

- The age of occurrence of the first VTE episode.
- The existence of a risk effector.
- The number of recurrent of VTE episodes.
- The presence of a family history.

Everyone who presented with first unprovoked episode of deep vein thrombosis at a young age and after the cancer diagnosis has been ruled out and is considered to be thrombophilic, regardless of whether or not there is a known thrombophilia and the risk of relapse is elevated. Thrombophilia check should not be massive. When a thrombophilia test is required, the investigation should include investigation for hematological disorders which at least doubling the risk of VTE.

The most common of them are major thrombophilic mutations, deficiencies of normal inhibitors of coagulation, and the diagnosis of the antiphospholipid syndrome. If none of the common disorders associated with hereditary or acquired thrombophilia is found, investigation may be extended to other rare mutations or a combination of polymorphisms or to find out other acquired conditions that increase the risk of VTE.

In any case, the investigation and the result evaluation should not be nonselective in population groups that do not fall under the criteria listed below. Laboratory investigation of hematologic disorders associated with hereditary or acquired thrombophilia includes:

1. Complete blood count.
2. Measurement of PT and aPTT.
3. Measurement of normal coagulation inhibitor levels:
    a. Antithrombin (AT).
    b. Protein C (PC).
    c. Protein S (PS).
4. Test for the presence of resistance to activated protein C (APC-resistance) associated with Leiden factor V mutation.
5. Control for the presence of the G20210A mutation in the prothrombin gene (FIIG20210A).
6. Check for the presence of lupus anticoagulant, anticardiolipin antibodies, and antibodies against β2 glycoprotein I (anti-β2-GP1) [56, 70–74].

9. When should thrombophilia investigation take place?

Control for mutation of factor V Leiden or the G20210A mutation in the prothrombin gene using PCR methods can be applied at any time relatively to the

thrombotic episode and regardless of the administration of anticoagulant treatment. The levels of natural inhibitors of clotting are reduced in the acute phase of thrombosis (decrease in PS), pregnancy and labor (decrease in PS), and treatment with estrogenic contraceptives (reduction of PS).

PC and PS are reduced during treatment with vitamin K antagonists or when there is deficiency of vitamin K that is not associated with coumarin therapy. Administration of classical heparin causes a decrease in AT levels. The presence of hepatopathy, among other coagulation disorders, also causes a reduction in natural inhibitors. The presence of nephrotic syndrome causes a decrease in AT levels.

The timing methods of clotting are affected by the newer anticoagulants that are active after oral administration and specifically inhibit thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban).

As a result, during treatment with these drugs, it is not necessary to measure the levels of protein S and control for the presence of activated protein C resistance or the presence of lupus anticoagulant [56, 70–74].

10. PC and PS deficiency should be accomplished at least 2 months after cessation antagonist vitamin K treatment

Diagnosis of the inherited lack of AT, PC, or PS should only be performed if all conditions that lead to their acquired lack are excluded. Examination of the antiphospholipid syndrome can also be performed during the acute phase of VTE during anticoagulation treatment with classical heparin, low molecular weight heparin, or fondaparinux, if a suitable method for controlling the lupus anticoagulant is selected and weighted to the minimum concentration of heparin or fondaparinux or INR, which does not affect it. Therefore, at least in patients taking its antagonist vitamin K, test for the lupus anticoagulant should be done in a specialized laboratory.

In women with obstetric complications (such as miscarriages, preeclampsia, endometrial deaths, etc.), the investigation for obstetric antiphospholipid syndrome is preferable to occur close to the episode because it is possible for the levels of antiphospholipid antibodies to fall as far as we go away from pregnancy [56, 70–74].

11. Patients which is recommended for thrombophilia investigation

According to the international guidelines, the laboratory investigation for the presence of hereditary or acquired thrombophilia is recommended in the following cases:

- In patients with the first VTE episode occurred at the age of less than 40 years.
- In patients younger than 60 years of age who present the first VTE episode without the presence of a significant risk factor or a known endogenous risk factor for VTE.
- In patients who present as a single risk factor for VTE, oral contraceptive, or hormone replacement therapy or pregnancy.
- Laboratory testing by techniques other than molecular biology (PCR) techniques for hereditary causes of thrombophilia should be performed at least 2 months after the stop of hormone therapy or labor [56, 70–74].

- In patients with relapsing VTE, regardless of the presence of risk factors.
- In patients without varicose veins exhibiting recurrent superficial thrombophlebitis.
- In patients with VTE in unusual sites, such as retinal vein thrombosis or cerebral or mesenteric or hepatic vein thrombosis.
- In patients with warfarin-induced skin necrosis and neonates with purpura fulminans not related with sepsis.
- In asymptomatic relatives of first-degree patients with proven symptomatic thrombophilia or hematologic disorder that is linked with hereditary thrombophilia.
- In women with a family history of adjusted VTE at <60 years, going to take hormonal medications for assisted reproduction.
- In women with a history of recurrent unexplained abortions, growth retardation, or endometrial death.

The results of hematologic control should be analyzed by a hematologist. Patients with hereditary or acquired thrombophilia should be monitored by a hematology center. Screening for thrombophilia is not recommended in women who are going to take contraceptive treatment and in women who are going to undergo in vitro fertilization techniques if they do not meet any of the previous criteria or familial history of thromboembolism [56, 70–74].

12. Conclusions

Considering all the risks and major obstetrics complications that thromboembolic events can lead during pregnancy, we can conclude that cooperation among obstetricians and hematologists is crucial for better outcomes. The careful history and appropriate laboratory investigation consist of the key point for the management of these patients.

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References

[1] Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ 3rd. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: A 30-year population-based study. Annals of Internal Medicine. 2005;**143**(10):697-706

[2] James AH. Venous thromboembolism in pregnancy. Arteriosclerosis, Thrombosis, and Vascular Biology. 2009;**29**(3):326-331. DOI: 10.1161/ATVBAHA.109.184127

[3] James AH. Pregnancy and thrombotic risk. Critical Care Medicine. 2010;**38**(2 Suppl):S57-S63. DOI: 10.1097/CCM.0b013e3181c9e2bb

[4] Rosendaal FR. Thrombosis in the young: Epidemiology and risk factors. A focus on venous thrombosis. Thrombosis and Haemostasis. 1997; **78**(1):1-6

[5] James AH. Prevention and management of venous thromboembolism in pregnancy. The American Journal of Medicine. 2007;**120** (10 Supp. 2):S26-S34

[6] James AH, Brancazio LR, Ortel TL. Thrombosis, thrombophilia, and thromboprophylaxis in pregnancy. Clinical Advances in Hematology & Oncology. 2005;**3**(3):187-197

[7] Vormittag R, Pabinger I. Thrombophilia and pregnancy complications. Hämostaseologie. 2006; **26**(1):59-62

[8] Pabinger I. Thrombophilia and its impact on pregnancy. Thrombosis Research. 2009;**123**(Supp. 3):S16-S21. DOI: 10.1016/S0049-3848(09)70128-8

[9] McColl MD, Walker ID, Greer IA. The role of inherited thrombophilia in venous thromboembolism associated with pregnancy. British Journal of Obstetrics and Gynaecology. 1999; **106**(8):756-766

[10] Zotz RB, Gerhardt A, Scharf RE. Inherited thrombophilia and gestational venous thromboembolism. Best Practice & Research. Clinical Haematology. 2003;**16**(2):243-259

[11] Martinelli I, De Stefano V, Taioli E, Paciaroni K, Rossi E, Mannucci PM. Inherited thrombophilia and first venous thromboembolism during pregnancy and puerperium. Thrombosis and Haemostasis. 2002;**87**(5):791-795

[12] Martinelli I, Legnani C, Bucciarelli P, Grandone E, De Stefano V, Mannucci PM. Risk of pregnancy-related venous thrombosis in carriers of severe inherited thrombophilia. Thrombosis and Haemostasis. 2001;**86**(3):800-803

[13] Coppens M, Kaandorp SP, Middeldorp S. Inherited thrombophilias. Obstetrics and Gynecology Clinics of North America. 2006;**33**(3):357-374. Review

[14] Coppens M, van de Poel MH, Bank I, Hamulyak K, van der Meer J, Veeger NJ, et al. A prospective cohort study on the absolute incidence of venous thromboembolism and arterial cardiovascular disease in asymptomatic carriers of the prothrombin 20210A mutation. Blood. 2006;**108**(8): 2604-2607. Epub 2006 Jun 15

[15] Bank I, Libourel EJ, Middeldorp S, Van Pampus EC, Koopman MM, Hamulyák K, et al. Prothrombin 20210A mutation: A mild risk factor for venous thromboembolism but not for arterial thrombotic disease and pregnancy-related complications in a family study. Archives of Internal Medicine. 2004; **164**(17):1932-1937

[16] McColl MD, Ramsay JE, Tait RC, Walker ID, McCall F, Conkie JA, et al.

Risk factors for pregnancy associated venous thromboembolism. Thrombosis and Haemostasis. 1997;**78**(4):1183-1188

[17] Tan JY. Thrombophilia in pregnancy. Annals of the Academy of Medicine, Singapore. 2002;**31**(3): 328-334

[18] Kutteh WH, Triplett DA. Thrombophilias and recurrent pregnancy loss. Seminars in Reproductive Medicine. 2006;**24**(1): 54-66

[19] Vucić N, Frleta M, Petrović D, Ostojić V. Thrombophilia, preeclampsia and other pregnancy complications. Acta Medica Croatica. 2009;**63**(4): 297-305

[20] Pabinger I. Thrombophilia and its impact on pregnancy. Hämostaseologie. 2008;**28**(3):130-134

[21] Parunov LA, Soshitova NP, Ovanesov MV, Panteleev MA, Serebriyskiy II. Epidemiology of venous thromboembolism (VTE) associated with pregnancy. Birth Defects Research. Part C, Embryo Today. 2015;**105**(3): 167-184. DOI: 10.1002/bdrc.21105. Epub 2015 Sep 25

[22] Oger E, Mottier D. Incidence and risk factors for venous thromboembolism. La Revue du Praticien. 2007;**57**(7). 711-3, 716, 719-20

[23] Ducloy-Bouthors AS, Trillot N. Risk factors of thromboembolism associated with pregnancy and the puerperium. Role of inherited and acquired thrombophilia. Annales de Médecine Interne. 2003;**154**(5–6):295-300

[24] McColl MD, Ramsay JE, Tait RC, et al. Superficial vein thrombosis: Incidence in association with pregnancy and prevalence of thrombophilic abnormalities. Thrombosis and Haemostasis. 1998;**79**:741-742

[25] Vossen CY, Preston FE, Conard J, Fontcuberta J, Makris M, van der Meer FJ, et al. Hereditary thrombophilia and fetal loss: A prospective follow-up study. Journal of Thrombosis and Haemostasis. 2004;**2**(4):592-596

[26] Martinelli I, Mannucci PM, De Stefano V, Taioli E, Rossi V, Crosti F, et al. Faioni EM different risks of thrombosis in four coagulation defects associated with inherited thrombophilia: A study of 150 families. Blood. 1998; **92**(7):2353-2358

[27] Dahlbäck B. The discovery of activated protein C resistance. Journal of Thrombosis and Haemostasis. 2003; **1**(1):3-9

[28] Dahlbäck B. Early days of APC resistance and FV Leiden. Hämostaseologie. 2008;**28**(3):103-109

[29] Castoldi E, Rosing J. APC resistance: Biological basis and acquired influences. Journal of Thrombosis and Haemostasis. 2010;**8**(3):445-453. DOI: 10.1111/ j.1538-7836.2009.03711.x. Epub 2009 Nov 30

[30] Segers K, Dahlbäck B, Nicolaes GA. Coagulation factor V and thrombophilia: Background and mechanisms. Thrombosis and Haemostasis. 2007; **98**(3):530-542

[31] Castoldi E, Rosing J. Factor V Leiden: A disorder of factor V anticoagulant function. Current Opinion in Hematology. 2004;**11**(3):176-181

[32] Brugge JM, Simioni P, Bernardi F, Tormene D, Lunghi B, Tans G, et al. Expression of the normal factor V allele modulates the APC resistance phenotype in heterozygous carriers of the factor V Leiden mutation. Journal of Thrombosis and Haemostasis. 2005; **3**(12):2695-2702

[33] Segers O, Simioni P, Tormene D, Bulato C, Gavasso S, Rosing J, et al.

Genetic modulation of the FV(Leiden)/ normal FV ratio and risk of venous thrombosis in factor V Leiden heterozygotes. Journal of Thrombosis and Haemostasis. 2012;**10**(1):73-80

[34] Martinelli I. von Willebrand factor and factor VIII as risk factors for arterial and venous thrombosis. Seminars in Hematology. 2005;**42**(1):49-55

[35] Bank I, Libourel EJ, Middeldorp S, Hamulyák K, van Pampus EC, Koopman MM, et al. Elevated levels of FVIII:C within families are associated with an increased risk for venous and arterial thrombosis. Journal of Thrombosis and Haemostasis. 2005;**3**(1):79-84

[36] Eid SS. Hereditary deficiencies of antithrombin III, protein S, and the protein C pathway in Jordanian thrombosis patients. Clinical Laboratory Science. 2002;**15**(4):196-199

[37] Ichiyama M, Ohga S, Ochiai M, Tanaka K, Matsunaga Y, Kusuda T, et al. Age-specific onset and distribution of the natural anticoagulant deficiency in pediatric thromboembolism. Pediatric Research. 2016;**79**(1–1):81-86. DOI: 10.1038/pr.2015.180. Epub 2015 Sep 15

[38] Caspers M, Pavlova A, Driesen J, Harbrecht U, Klamroth R, Kadar J, et al. Deficiencies of antithrombin, protein C and protein S—Practical experience in genetic analysis of a large patient cohort. Thrombosis and Haemostasis. 2012; **108**(2):247-257. DOI: 10.1160/TH11-12-0875. Epub 2012 May 25

[39] Wypasek E, Undas A, Protein C. Protein S deficiency—Practical diagnostic issues. Advances in Clinical and Experimental Medicine. 2013;**22**(4): 459-467

[40] Campello E, Spiezia L, Radu CM, Bulato C, Gavasso S, Tormene D, et al. Circulating microparticles and the risk of thrombosis in inherited deficiencies of antithrombin, protein C and protein S. Thrombosis and Haemostasis. 2016; **115**(1):81-88. DOI: 10.1160/TH15-04-0286. Epub 2015 Sep 10

[41] Hotoleanu C. Genetic risk factors in venous thromboembolism. Advances in Experimental Medicine and Biology. 2017;**906**:253-272

[42] Crowther MA, Kelton JG. Congenital thrombophilic states associated with venous thrombosis: A qualitative overview and proposed classification system. Annals of Internal Medicine. 2003;**138**(2):128-134

[43] Poli D, Gensini GF. Antiphospholipid syndrome and venous thromboembolism: The role of congenital thrombophilia. Annali Italiani di Medicina Interna. 2005;**20**(4): 218-223

[44] Hague WM. Homocysteine and pregnancy. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2003;**17**(3):459-469

[45] Campello E, Spiezia L, Radu CM, Gavasso S, Zerbinati P, Woodhams B, et al. Circulating microparticles in carriers of prothrombin G20210A mutation. Thrombosis and Haemostasis. 2014;**112**(3):432-437. DOI: 10.1160/ TH13-12-1006. Epub 2014 May 8

[46] März W, Nauck M, Wieland H. The molecular mechanisms of inherited thrombophilia. Zeitschrift für Kardiologie. 2000;**89**(7):575-586

[47] Unlü Y, Keleş S, Becit N, Koçoğullari CU, Koçak H, Bakan E. Hyperhomocysteinaemia as a risk factor for deep-vein thrombosis. European Journal of Vascular and Endovascular Surgery. 2005;**30**(3):315-318

[48] Quéré I, Gris JC, Dauzat M. Homocysteine and venous thrombosis. Seminars in Vascular Medicine. 2005; **5**(2):183-189

[49] Holmes VA. Changes in haemostasis during normal pregnancy: Does homocysteine play a role in maintaining homeostasis? The Proceedings of the Nutrition Society. 2003;**62**(2):479-493

[50] Zotz RB, Gerhardt A, Scharf RE. Pregnancy-associated venous thromboembolic disease: Prediction, prevention, and therapy. Hämostaseologie. 2006;**26**(1):63-71

[51] Couto E, Nomura ML, Barini R, Pinto e Silva JL. Pregnancy-associated venous thromboembolism in combined heterozygous factor V Leiden and prothrombin G20210A mutations. São Paulo Medical Journal. 2005;**123**(6): 286-288. Epub 2006 Jan 20

[52] Dobesh PP, Wittkowsky AK, Stacy Z, Dager WE, Haines ST, Lopez LM, et al. Key articles and guidelines for the prevention of venous thromboembolism. Pharmacotherapy. 2009;**29**(4):410-458

[53] Deitelzweig SB. Management and prevention of venous thromboembolism including surgery and the pregnant state. The Ochsner Journal. 2002;**4**(1): 23-29

[54] McFadden PM, Ochsner JL. A history of the diagnosis and treatment of venous thrombosis and pulmonary embolism. The Ochsner Journal. 2002; **4**(1):9-13

[55] Croles FN, Nasserinejad K, Duvekot JJ, Kruip MJ, Meijer K, Leebeek FW. Pregnancy, thrombophilia, and the risk of a first venous thrombosis: Systematic review and bayesian meta-analysis. BMJ. 2017;**359**:j4452

[56] Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest. 2008; **133**(6 Suppl):844S-886S. DOI: 10.1378/ chest.08-0761

[57] Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: The seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest. 2004; **126**(3 Suppl):627S-644S

[58] Wu O, Robertson L, Twaddle S, Lowe GD, Clark P, Greaves M, et al. Screening for thrombophilia in high-risk situations: Systematic review and cost-effectiveness analysis. The thrombosis: Risk and economic Assessment of thrombophilia screening (TREATS) study. Health Technology Assessment. 2006;**10**(11):1-110

[59] Robertson L, Wu O, Greer I. Thrombophilia and adverse pregnancy outcome. Current Opinion in Obstetrics & Gynecology. 2004;**16**(6):453-458

[60] Robertson L, Wu O, Langhorne P, Twaddle S, Clark P, Lowe GD, et al. Thrombosis: Risk and economic assessment of thrombophilia screening (TREATS) study. Thrombophilia in pregnancy: A systematic review. British Journal of Haematology. 2006;**132**(2): 171-196

[61] Ziakas PD, Poulou LS, Pavlou M, Zintzaras E. Thrombophilia and venous thromboembolism in pregnancy: A meta-analysis of genetic risk. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2015;**191**:106-111. DOI: 10.1016/j.ejogrb.2015.06.005. Epub 2015 Jun 16

[62] Pirtskhelani N, Kochiashvili N, Makhaldiani L, Pargalava N, Gaprindashvili E, Kartvelishvili K. Impact of inherited thrombophilia on the risk of recurrent venous thromboembolism onset in Georgian population. Georgian Medical News. 2014;**227**:93-97

[63] Pritchard AM, Hendrix PW, Paidas MJ. Hereditary thrombophilia and

recurrent pregnancy loss. Clinical Obstetrics and Gynecology. 2016;**59**(3): 487-497

[64] Lee SY, Kim EK, Kim MS, Shin SH, Chang H, Jang SY, et al. The prevalence and clinical manifestation of hereditary thrombophilia in Korean patients with unprovoked venous thromboembolisms. PLoS One. 2017;**12**(10):e0185785. DOI: 10.1371/journal.pone.0185785. eCollection 2017

[65] Mannucci PM, Franchini M. The real value of thrombophilia markers in identifying patients at high risk of venous thromboembolism. Expert Review of Hematology. 2014;**7**(6): 757-765. DOI: 10.1586/ 17474086.2014.960385. Epub 2014 Sep 18

[66] Howley HE, Walker M, Rodger MA. A systematic review of the association between factor V Leiden or prothrombin gene variant and intrauterine growth restriction. American Journal of Obstetrics and Gynecology. 2005;**192**(3):694-708. Review Br J Haematol. 2005 Oct;131(1): 80-90

[67] Eubanks AA, Deering SH, Thiel LM Risk Assessment and treatment guide for obstetric thromboprophylaxis: Comprehensive review of current guidelines. American Journal of Perinatology. Jan 2019;**36**(2):130-135 DOI: 10.1055/s-0038-1672164. [Epub 2018 Sep 19]

[68] Wu O, Greer IA. Is screening for thrombophilia cost-effective? Obstetrics and Gynecology Clinics of North America. 2006;**33**(3):389-395

[69] ACOG practice bulletin No. 197: Inherited Thrombophilias in pregnancy. [No authors listed]. Obstetrics and Gynecology. 2018;**132**(1):e18-e34. DOI: 10.1097/AOG.0000000000002703

[70] Romero A, Alonso C, Rincón M, Medrano J, Santos JM, Calderón E, et al. Risk of venous thromboembolic disease in women A qualitative systematic review. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2005;**121**(1):8-17. Review

[71] Alfirevic Z, Roberts D, Martlew V. How strong is the association between maternal thrombophilia and adverse pregnancy outcome? A systematic review. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2002;**101**(1):6-14. Review

[72] Morrison ER, Miedzybrodzka ZH, Campbell DM, Haites NE, Wilson BJ, Watson MS, et al. Prothrombotic genotypes are not associated with pre-eclampsia and gestational hypertension: Results from a large population-based study and systematic review. Thrombosis and Haemostasis. 2002; **87**(5):779-785. Review

[73] Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest. 2012; **141**(2 Suppl):e691S-e736S. DOI: 10.1378/chest.11-2300

[74] Kujovich JL. Thrombophilia and pregnancy complications. American Journal of Obstetrics and Gynecology. 2004;**191**(2):412-424. Review

Chapter 7

Peripartum Pulmonary Embolism

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Abstract

Pregnancy and peripartum increase the risk of venous thromboembolism (VTE) by many folds. Interestingly, the VTE is more common during the pregnancy, whereas the pulmonary embolism is more frequent in postpartum period. There are various risk factors for the VTE and pulmonary embolism in these patients. The important risks are improper thromboprophylaxis, obesity, and multigravida. The clinical parameters and the d-dimer are not used for diagnosis of thromboembolism during pregnancy and in the postpartum period. The compression ultrasonography (CUSG) is commonly used for VTE diagnosis; for the pulmonary embolism diagnosis, one has to consider the radiation hazard to the fetus as well as to the mothers. Ventilation/perfusion scan is the imaging of choice for patient who has respiratory signs with normal chest radiograph. If chest X-ray is abnormal with suspicion of peripartum pulmonary embolism (PPE), the choice should be computed tomographic angiography. Heparin and its derivatives remained the anticoagulation of choice for the treatment of VTE as well as the PPE, as it is a shorter acting, easy to reverse with protamine sulfate. Proper thromboprophylaxis is the key for prevention of VTE and peripartum pulmonary embolism.

Keywords: computed tomography, heparin, low-molecular-weight heparin, pregnancy, peripartum, pulmonary embolism, thrombolysis, ultrasound, ventilation/perfusion scan and warfarin

1. Introduction

The first description of a case compatible with deep venous thrombosis (DVT) appears during the Middle Ages: Guillaume de Saint-Pathus in 1271 reported as "La vie et les miracles de Saint Louis." It was about a 20-year-old Norman cobbler who suffered unilateral pain and swelling of the right calf that subsequently extended up to the thigh, and his surgeon advised him to wait and see. Patient's symptoms worsened, and he developed a leg ulcer. He was advised to visit the tomb of King Saint Louis. He spent days praying near the tomb and then decides to collect the dust below the stone covering the tomb and applied it directly to the ulcer. He was miraculously healed after this direct application and reported to survive. On the basis of the writings from the New Testament, Brenner surmised that Jesus Christ himself may have suffered from a pulmonary embolism (PE), but this hypothesis

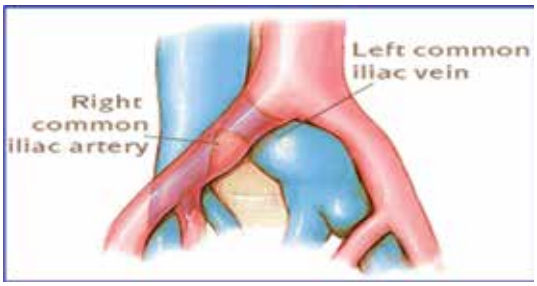

Figure 1.
May-Thurner Syndrome (narrowing of left iliac vein by crossing right iliac artery).

is debated. Avicenna warned against the risk of "particle migration" after the vein surgery: consistent with embolization of a DVT [1]. During the Renaissance physicians hypothesized that pregnancy-related DVT, which was the leading or even only cause of reported DVT at that time, was the consequence of retention of "evil humors." It was also thought that postpartum DVT was caused by retention of unconsumed milk in the legs ("milk leg"). Thus in the 1700s, breastfeeding was encouraged to prevent DVT, and bloodletting technique was used to treat DVT [1]. Virchow in 1856 demonstrated the relationship between DVT and fatal PE. The major pathologic mechanisms of venous thrombosis were first summarized in the famous Virchow's triad theorized by Andral in 1831, and in the 1920s, a consensus appeared regarding the three factors contributing to thrombosis: stasis, vessel wall alteration, and hypercoagulability: during this period a number of treatment breakthroughs were discovered by accident revolutionizing the DVT management [1].

Patients in pregnancy and postpartum are at the higher risk of thromboembolic phenomenon, particularly postpartum period. These risks are due to the normal or physiological changes of pregnancy to save the blood loss of parturition. These physiological changes will lead to the Virchow's triad. The peripartum pulmonary embolism (PPE) is 10 times more common than the nonpregnant females in the same age group. The risk of PPE increases by 20-fold in the postpartum period [2]. The incidence of pulmonary embolism during pregnancy and postpartum is 1.59 per 100,000 maternities. The venous thromboembolism (VTE) complicates 1–2/1000 pregnancies. Interestingly the VTE is common throughout all trimesters of pregnancies in contrast to pulmonary embolism which is most common in the postpartum period [3]. As described above, the VTE is equally distributed in all three trimesters of pregnancy; it is frequent in pelvic/iliofemoral veins and more common on the left side as there is compression on left iliac vein which is crossed by the right common iliac artery called May-Thurner syndrome (**Figure 1**). This is in contrast to the nonpregnant females where the VTE is common in the popliteal femoral venous system [4].

2. Risk factors

There are various risk factors for VTE and PPE in pregnancy and postpartum period. These risk factors are divided into three categories as follows (**Table 1**).

High-risk patients are mainly those patients with previous history of VTE, congenital, and acquired thrombophilia pregnant patients. The obstetric risk factors for VTE are multiple pregnancies, surgical delivery, and patients with the postpartum hemorrhage. The transient risk factors for the development of VTE and PPE are ovarian hyperstimulation syndrome, hyperemesis gravidarum, severe dehydration, surgical interventions, and immobility. There can be more than one risk factor for VTE in one patient. Obesity and multiple pregnancies were the risk factors for VTE in Middle East population [5].

Higher risk
Congenital or acquired thrombophilia
History of VTE
Obesity
Multigravida
Maternal smoking
Elderly parturient
Obstetric risk
Multiple pregnancies
Assisted reproduction
Cesarean section
Postpartum hemorrhage
Transient risk
Ovarian hyperstimulation syndrome
Hyperemesis gravidarum
Surgical intervention in the peripartum
Immobility
Systemic infections

Table 1.
Categories of risk for VTE in pregnancy.

3. Pathophysiology

The various physiological changes of pregnancy in combination with venous stasis and vascular injury (normal delivery as well as surgical deliveries) will form the Virchow's triad and a higher risk for thromboembolic phenomenon in pregnancy and postpartum period.

Venous stasis results from a hormonally induced decrease in venous tone and obstruction of venous flow by the enlarging uterus. A reduction of venous flow velocity of 50% occurs in the legs by 29 weeks of gestation and remains up to 6 weeks postpartum. In pregnant and postpartum women, the left lower extremity is the most common site of DVT. The anatomic reasons (compression of the left common iliac vein by the right common iliac artery which is accentuated by the enlarging uterus) have been attributed [6]. Endothelial damage in the pelvic veins occurs from the delivery or from venous hypertension. Normal pregnancy induces a hypercoagulable state. This hypercoagulable state is multifactorial and is thought to be due to a combination of physical and hormonal factors and hematologic changes. The physical and hormonal changes of pregnancy begin early in the first trimester. Progesterone-mediated increases in venous distensibility and capacity are apparent in the first trimester that result in increased venous stasis [6].

During pregnancy there will be increased in procoagulant factor concentration (factor VII, VIII, X, and vWF); there is a fivefold increase in the plasminogen activator inhibitor type 1 levels, whereas there is a decrease in natural anticoagulant particularly protein S and the fibrinogen levels. There is an increased resistance to protein C activity. These changes during pregnancy and parturition are for the protection from massive blood loss during delivery. The dark side of it is that it increases the risk for VTE and pulmonary embolism during pregnancy and in the peripartum period [7].

Pulmonary embolism (PE) can occur if venous thrombi detach and emblaze to the pulmonary circulation. It causes pulmonary vascular occlusion and impairs gas exchange and circulation. Larger emboli wedge in the main pulmonary artery, whereas smaller emboli occlude the peripheral arteries and peripheral PE can

cause pulmonary infarction. Obstruction of the pulmonary flow creates dead space ventilation due to alveolar ventilation exceeds pulmonary capillary blood flow. This contributes to ventilation-perfusion mismatch with increasing in pulmonary vascular resistance. As the pulmonary artery systolic pressure increases, the right ventricular afterload increases leading to a right ventricular impairment. When right ventricular failure progresses, the left ventricular filling may be impaired, and it may rapidly progress to myocardial ischemia which may occur secondary to inadequate coronary artery filling with potential for hypotension, syncope, electromechanical dissociation, or sudden death. The humoral mediator serotonin and thromboxane are released from activated platelets and trigger vasoconstriction in the healthy lungs [6].

4. Diagnosis

It is of vital importance to accurately diagnose the VTE and PPPE to avoid the misdiagnosis and increase the morbidity and mortality, whereas when falsely diagnosed, it will unnecessarily increase the risk of bleeding and increased morbidity and mortality.

The clinical manifestations such as tachypnea, dyspnea, and tachycardia may be considered as related to pregnancy. The d-dimer are not of help in pregnant and postpartum patients, as it raises changes of normal pregnancy and takes weeks in postpartum to return to the normal limits [8].

Arterial blood gas (ABG) may show respiratory alkalosis, and 12 lead ECG may be useful as it may show changes in right-sided leads. These tests are neither sensitive nor specific in the diagnosis of pulmonary embolism.

4.1 Echocardiography

Echocardiography is a noninvasive procedure and may show the indirect signs called "McConnell" sign that is the right ventricular hypokinesia and hypercontractility of the apical wall with raised pressures [9]. Echocardiograph also helps in rule of other possible etiologies such as peripartum cardiomyopathy.

Imaging studies are the corner stone for the diagnosis of the pulmonary embolism; it is of vital importance that while considering the selection of imaging studies, one has to be very careful in its effects not only on fetus but equally important for mothers as well.

4.2 Chest X-ray

All patients suspected of PE will have a chest X-ray; in pregnant patient we can cover the abdomen and do a chest X-ray. Normal chest X-ray with respiratory symptoms should raise the high index of suspicion for the pulmonary embolism. Presence of the wedge-shaped opacity with pleural base is considered as hallmark for the diagnosis of PE in chest X-ray, but this also found to be not sensitive or specific for the pulmonary embolism [10].

4.3 Bilateral compression sonography

Bilateral compression sonography of the lower limbs has an advantage of portability, noninvasive and no radiations; at the same time it diagnoses the VTE with accuracy. If it is positive and shows thromboembolic lesion, we have to start the anticoagulation therapy. But if it is negative, then we have to proceed with further diagnostic imaging studies [11].

4.4 Ventilation/perfusion (V/Q) scan

Those pregnant and postpartum patients with normal chest X-ray and suspected to have PPPE, the ventilation/perfusion (V/Q) scan is the imaging of choice. A positive V/Q scan will demonstrate a mismatch perfusion pattern. The low and high probability scans are diagnostic, as the low probability scan has up to 6% chances of having pulmonary embolism, whereas the high probability scan had up to 96% chances of PE. As most of the parturient are healthy with a normal chest X-ray, the V/Q scan has a higher diagnostic accuracy for the diagnosis of PE [12].

4.5 CT pulmonary angiography (CTPA)

CTPA is increasingly used, and it is a sensitive and specific imaging study for the diagnosis of the pulmonary embolism in both pregnant and nonpregnant patients (**Figure 2**). It is also an imaging study of choice in patients suspected of pulmonary embolism with an abnormal chest X-ray as it gives alternative diagnosis if there is no pulmonary embolism. In pregnant patients, there is an increase in cardiac output and blood volume; hence, there can be issues with quantification and time of intravenous contrast is difficult [13].

4.6 Magnetic resonance pulmonary angiography (MRPA)

It is not much evaluated in pregnancy, despite of MRI contrast (gadolinium) has no evidence of causing fetal teratogenicity. In contrast, it is highly sensitive and specific in diagnosis of PE in the general population (up to 92% and up to 100%) [14].

4.7 Digital subtraction angiography (DSA)

It is a historical gold standard for the diagnosis of PE. It is rarely performed nowadays and it also not evaluated in the pregnant population. In retrospective subpopulation evaluation, it was found that the DSA is less sensitive than CTPA with a higher reports of false negativity [15].

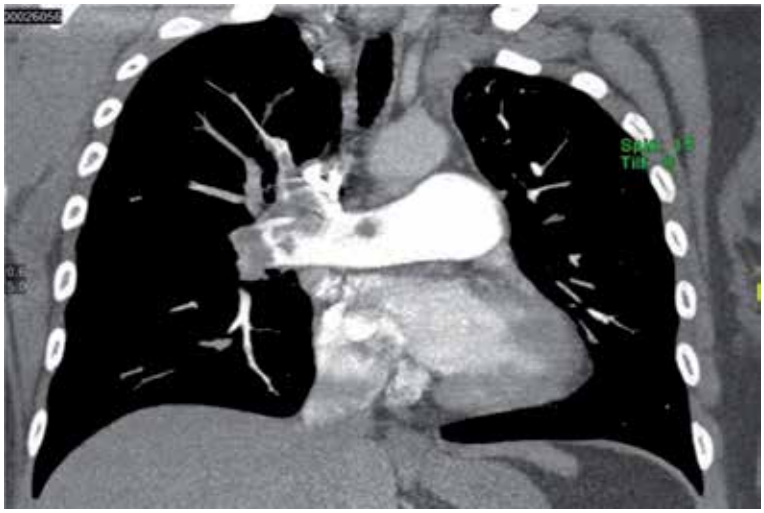

Figure 2.
CTPA showing pulmonary embolism.

In the concluding lines about the selection of imaging studies, the fear of fetal radiation exposure and adverse effects should not deprive the mother of timely and accurate diagnosis of PPE. Each of the imaging study has advantages and disadvantage (**Table 2**). Better approach is to follow the diagnostic algorithm (**Figure 3**) [16].

Imaging Study	Benefit	Risk
Computerized Tomographic Pulmonary Angiogram (CTPA)	Will show Thrombus, gives alternative diagnosis and lower fetal radiations	Higher breast radiations; use of contrast
Ventilation / perfusion Scan (V/Q Scan)	Lower maternal breast radiation	No Clinical Decisions or no alternative diagnosis
Compression Ultrasonography (CUS)	No radiations, Non Invasive; potential to detect deep venous thrombosis	Low sensitivity

Table 2.
Risk and benefits of various imaging studies.

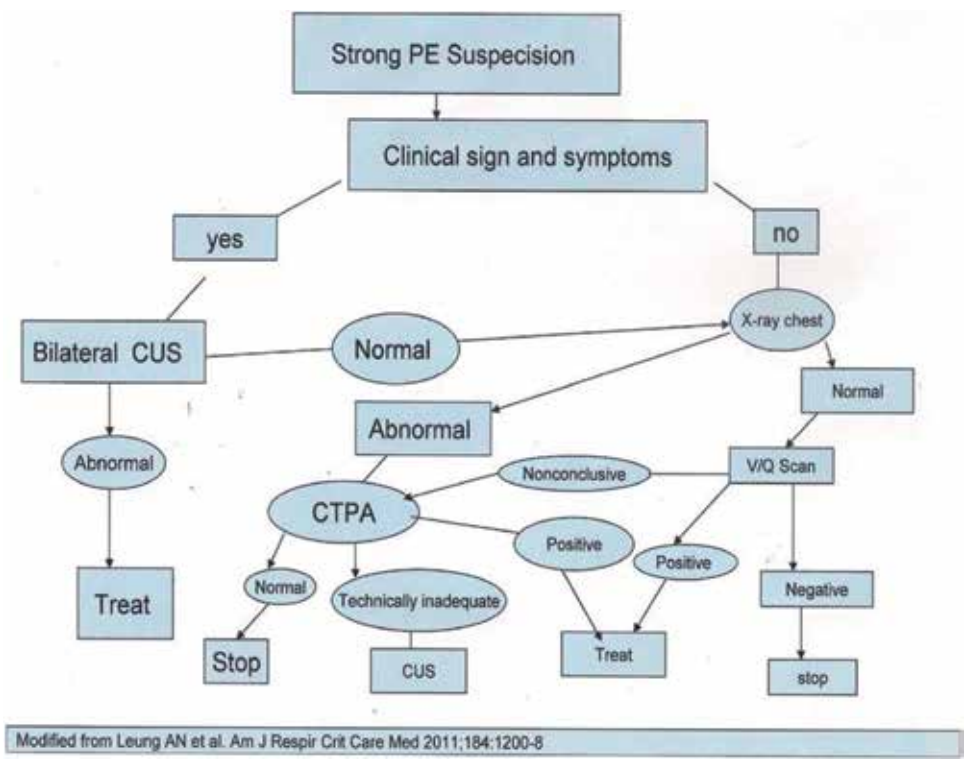

Figure 3.
Diagnostic algorithm for PPE.

The V/Q imaging is of choice when chest X-ray is normal; CTPA should have upper hand if chest X-ray is abnormal, but it had more radiation exposure to the maternal breast, with slightly increased risk of carcinoma, and it will increase the lifetime risk for breast cancer by 13.6% [17].

4.8 Single-photon emission CT ventilation/perfusion scan (SPECT V/Q)

The use of SPECT V/Q is superior to planar V/Q scintigraphy and CTPA. In nuclear medicine, the transition from planar techniques to SPECT has led to improvements in sensitivity and diagnostic accuracy. The published literature on SPECT V/Q has consistently shown improvements in sensitivity and specificity. The CTPA sensitivity in prospective multicenter PIOPED 2 study suggests that even with current-generation CT technology, CTPA fails to diagnose PE in approximately one in every six patients. If the limitations of CTPA in the detection of smaller emboli and larger emboli are missed, it is suggested that emboli not detected by CTPA are not clinically significant; it may not be true in patients with cardiorespiratory disease, and in these patients in particular, accurate detection is of vital importance. The PIOPED 2 study demonstrated that the CTPA accuracy falls further, if the scan results do not correlate with the clinical likelihood of disease, and in these circumstances, the incidence of false-positive and false-negative results is significant SPECT V/Q. Using Technegas also has the advantage of an extremely high-negative predictive value, reaching 98.5% in a large prospective series [18].

In PIOPED 2 study, over 40% of patients did not undergo CTPA because of renal impairment, contrast allergy, or too poor a state of health. This hardly endorses the notion that CTPA should be regarded as the primary screening test for the imaging of PE. Although CTPA has the advantage of being able to detect other lung diseases, it should be noted that V/Q scintigraphy can detect conditions other than PE [18].

V/Q scintigraphy in many countries continues to be done with planar imaging and using 133Xe as the ventilation agent. SPECT V/Q can be adequately performed with diethylenetriaminepentaacetic acid aerosols and in many in many countries. SPECT V/Q is clearly superior to planar imaging, and combined with recent developments in computing and camera hardware, V/Q SPECT also has the ability to quantify the extent of PE, and it is helpful in guiding treatment decisions [18]. Ventilation SPECT significantly increased the number of pregnant patients who could be classified as definitely positive or definitely negative. Only a minority of pregnant patients in the cohort had perfectly normal perfusion SPECT studies. A ventilation study is recommended as part of SPECT scintigraphy in pregnancy to improve diagnostic accuracy and reporter confidence. It also has a lower radiation dose to the mother [18].

5. Management

Heparin (indirect thrombin inhibitors) remained the commonly used anticoagulation medication in patients with thromboembolic phenomenon. It should be started when one suspected the diagnosis of pulmonary embolism. The advantages of unfractionated heparin (UFH) are shorter half-life, can be easily reversed, and have bigger molecular size; hence it cannot cross the placenta and no fetal adverse effects, and it is also not secreted into the breast milk. As there is increased blood volume during the pregnancy and peripartum period, increased heparin-binding proteins, and increased clearance of heparin through the renal system, the pregnant patient requires a higher dose of heparin to achieve the therapeutic levels. The dose of heparin may have to be increased to double to achieve the therapeutic effects [19]. The adverse effect of heparin, the fearsome, is the heparin-induced thrombocytopenia. It is divided into two types, the type 1 (also called heparin-associated thrombocytopenia or HAT) is

mainly benign condition and occurs due to negatively charged heparin that binds and destroys the positively charged platelets. HAT is a self-limiting clinical entity and does not require ant addition therapy. The HIT type 2 is immunologically mediated and can cause life-threatening thromboembolism, needs immunoassay or platelet aggregation test for diagnosis, and needs immediate stoppage of all forms of heparin to start direct thrombin inhibitors [20]. The osteopenia is another adverse effect of heparin use; it occurs due to inhibition of active metabolites of vitamin D. It increases the risk of fracture of the bones in pregnant patients [21].

5.1 Warfarin

Warfarin is a vitamin K antagonist commonly used anticoagulant in general population. It is a cost-effective medication. It is contraindicated in pregnancy as it crosses placenta and fetal teratogenic changes mainly the central nervous system defects. It also increases the risk of fetal miscarriages [22].

5.2 Thrombolysis and thrombectomy

In patients with massive pulmonary embolism causing hemodynamic deteriorations, hypoxia and right ventricular strain, immediate thrombolysis or thrombectomy is indicated (**Figure 4**) [16]. It may be associated with significant

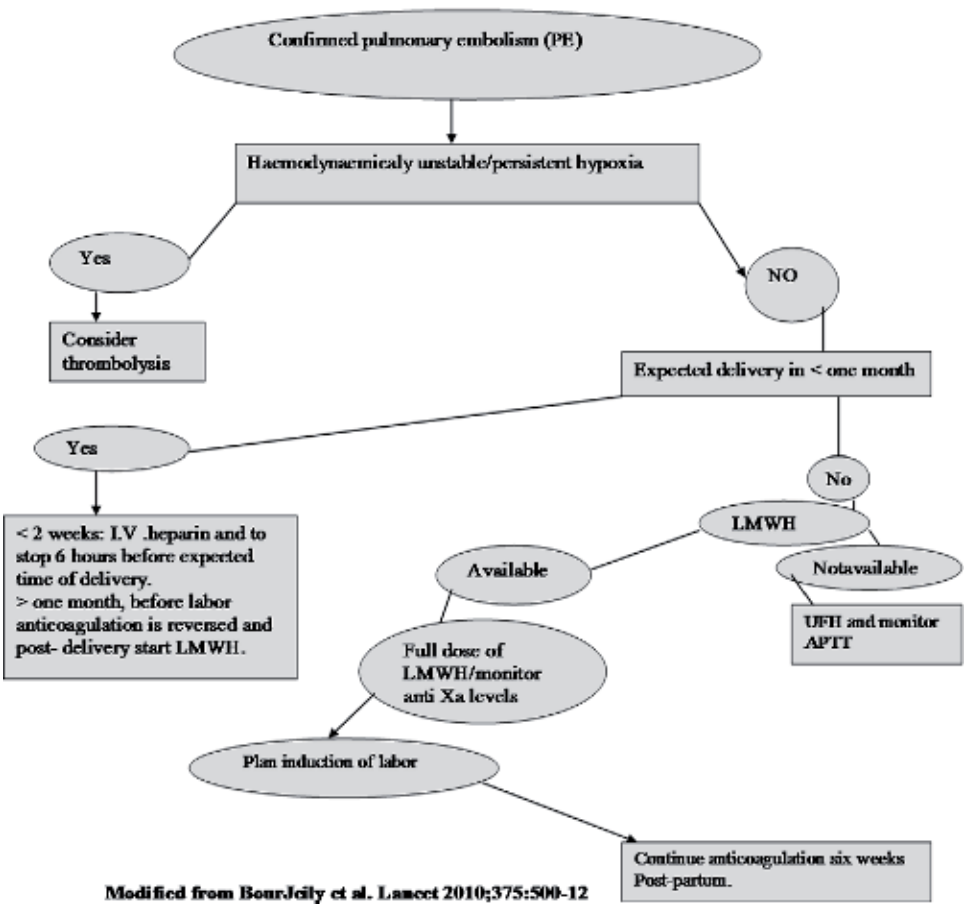

Figure 4.
Treatment of pulmonary embolism in pregnancy and postpartum.

bleeding risk in pregnant patients. A literature review found that the thrombolytic therapy in pregnancy is having a lower maternal mortality of around 1% and premature delivery and fetal loss of around 6%, which is significantly lower to the embolectomy where the fetal loss is reported up to 40%. Thrombolytic agent plasminogen activator is preferred as it does not cross placenta and does not generate antibodies [23].

Saeed et al. reviewed 13 patients with peripartum pulmonary embolism reported between 1970 and 2012, age was ranging from 21 to 39 years, and the clinical manifestations of PE were respiratory and cardiac dyspnea in nine patients, tachycardia in five, cyanosis in four, tachypnea in four, hypoxemia in two, acute respiratory distress in one, and palpitations in one patient. Heparin at therapeutic doses in nine patients was insufficient to resolve their unstable hemodynamic conditions. In all 13 patients, surgical pulmonary embolectomy was indicated because of rapidly worsening hemodynamics and cardiogenic shock. All patients underwent cardiopulmonary bypass. The thrombi were removed through an opening in the main PA in all patients. Two maternal deaths and three fetal deaths occurred leading to a 15.4% maternal mortality rate and 23% fetal mortality rate [24].

5.3 Inferior vena cava (IVC) filter

The IVC filter is indicated in patients with whom systemic anticoagulation is contraindicated or patients with recurrent embolization and patients developing recurrent embolization in spite of systemic anticoagulation. IVC filter is not free from complications, which includes perforation and migration to the surrounding structures [23].

5.4 Supportive care and vasopressors

Respiratory distress and hemodynamic instability in patients with peripartum pulmonary embolism may need invasive ventilation and hemodynamic support with vasopressors. Treating physician should be well aware of physiological changes in pregnancy. Normal blood pressure and partial pressure of carbon dioxide are lower in pregnancy. The position of the patient being nursed is again of vital importance; patient should be in lateral position to avoid IVC compression by the gravid uterus. The vasopressor should be used judiciously as they decrease the blood flow in uteroplacental circulation, whereas the persistent hypotension also poses a serious risk for the vital organ functions [25].

6. Differential diagnosis

The PPE should be differentiated from community-acquired pneumonia and peripartum cardiomyopathy. The echocardiogram will help in ruling out peripartum cardiomyopathy, and signs of sepsis will differentiate PPE from community-acquired pneumonia.

7. Prevention

Peripartum thromboembolism common, as still the prophylaxis, is adequately administered in high-risk patients [5]. Those patients with a higher risk of thromboembolism during pregnancy and peripartum should receive the thromboprophylaxis to prevent proper thromboembolisms (**Figure 5**).

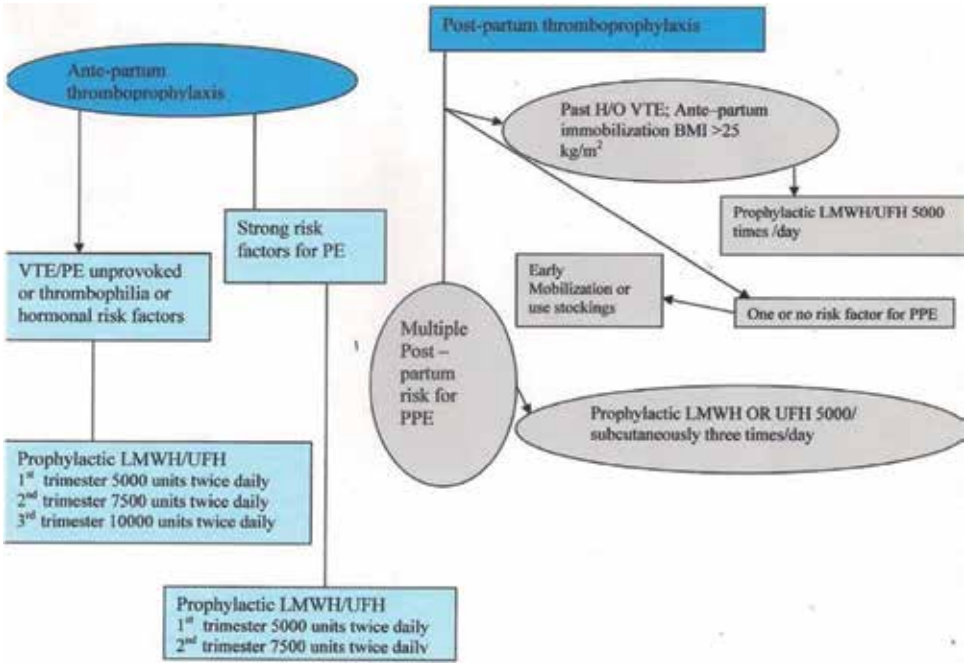

Figure 5.
Treatment of pulmonary embolism in the peripartum period (modified from Bourjeily et al. [26]).

8. Conclusion

The pregnant patients are at higher risk for VTE in all three trimester pregnancy, but in the postpartum period, they are at higher risk for the development of peripartum pulmonary embolism (PPE). The physiological changes of pregnancy and normal or surgical delivery will form Virchow's triad, hence increasing the risk of VTE by 20-folds. It is important to diagnose early and manage it properly to avoid increase in morbidity and mortality in these special groups of patients. The risk factors for VTE and pulmonary embolism in these patients are broadly categorized into high risk, obstetric risk, and transient risk factors. The diagnosis is an important aspect of the management of VTE and PPE. As the misdiagnosis will increase the morbidity and mortality, wrong diagnosis will expose these patients for unnecessary risk of hemorrhagic complications of the anticoagulant use. We have to consider the ration hazard to the fetus and mother, but at the same time, one should not deprive the mother of accurate and early diagnosis of PPE for the fear of radiations. Compression USG, V/Q scan, and CTPA can be used for the diagnosis of VTE and PPE depending on the chest conditions. PPE has to be differentiated from community-acquired pneumonia and peripartum cardiomyopathy. Heparin is the anticoagulation of choice in VTE and PPE; if patients develop heparin-induced thrombocytopenia (HIT), the choice is direct thrombin inhibitors. Warfarin has the teratogenic effect; it should not be used during the pregnancy. Risk evaluation and strict use of thromboprophylaxis will prevent or decrease the incidence of PPE and VTE.

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References

[1] Galanaud J-P, Laroche J-P, Righini M. The history and historical treatments of deep vein thrombosis. Journal of Thrombosis and Haemostasis. 2013;**11**:402-411

[2] Simcox LE, Ormesh L, Tower C, Green IA. Pulmonary thrombo-embolism in pregnancy: Diagnosis and management. Breathe. 2015;**11**:283-289

[3] Gehrman RB, Goodwin TM, Leung B, et al. Incidence, clinical characteristics and timing of objectively diagnosed venous thromboembolism during pregnancy. Obstetrics and Gynecology. 1999;**94**:730-734

[4] Jacobsen AF, Skjeldestad FE, Sandset PM. Incidence and risk pattern of venous thromboembolism in pregnancy and puerperium: A research based case control study. American Journal of Obstetrics and Gynecology. 2008;**198**:233 e1-233 e7

[5] Alsayegh F, Al-Jasser W, Wani S, Tahlak M, Al Bahar A, Al-Kharusi L, et al. Venous thromboembolism risk and adequacy of prophylaxis in high risk pregnancy in Arabian Gulf. Current Vascular Pharmacology. 2016;**14**:368-373

[6] Devis P, Knuttinen MG. Deep venous thrombosis in pregnancy: Incidence, pathogenesis and endovascular management. Cardiovascular Diagnosis and Therapy. 2017;**7**:S309-S319

[7] Bremme KA. Haemostatic changes in pregnancy. Best Practice & Research. Clinical Haematology. 2003;**16**(2):153-168

[8] Eichinger S. D-dimer testing in pregnancy. Seminars in Vascular Medicine. 2005;**5**(4):375-378

[9] López-Candales A, Edelman K, Candales MD. Right ventricular apical contractility in acute pulmonary embolism: The McConnell sign revisited. Echocardiography. 2010;**27**:614-620

[10] Worsley DF, Alavi A, Aronchick JM, et al. Chest radiographic finding in patients with acute pulmonary embolism. Observation from the PIOPED study. Radiology. 1993;**189**:133

[11] Garcia ND, Morasch MD, Ebaugh JL, Shah S, Blackburn D, Astleford P, et al. Is bilateral ultrasound scanning of the legs necessary for patients with unilateral symptoms of deep vein thrombosis? Journal of Vascular Surgery. 2001;**34**:792-797

[12] Ravel MP, Cohen S, Sanchez O, et al. Pulmonary embolism during pregnancy: Diagnosis with lung scintigraphy or CT angiography? Radiology. 2011;**258**:590

[13] Cahill AG, Stout MJ, Macones GA, Bhalla S. Diagnosis of pulmonary embolism in pregnancy using computed-tomographic angiography or ventilation perfusion. Obstetrics and Gynecology. 2009;**114**:124

[14] Pleszewski B, Chartrand-Lefebvre C, Qanadil SD, et al. Gadolinium-enhanced pulmonary magnetic resonance angiography in the diagnosis of acute pulmonary embolism: A prospective study of 48 patients. Clinical Imaging. 2006;**30**:166

[15] Wittram C, Waltman AC, Shepard JA, et al. Discordance between CT and angiography in PIOPEDII study. Radiology. 2007;**244**:883

[16] Shaikh N, Ummunnisa F, Aboobacker N, Gazali M, Kokash O. Peripartum pulmonary embolism: Anesthetic and surgical considerations. Open Journal of Obstetrics and Gynecology. 2013;**3**:158-164. DOI: 10.4236/ojog.2013.31A030

[17] Remy-Jordin M, Remy J. Spiral Ct angiography of the pulmonary circulation. Radiology. 1999;**212**:615-636

[18] Grüning T, Mingo RE, Gosling MG, Farrell SL, Drake BE, Loader RJ, et al. Diagnosing venous thromboembolism in pregnancy. The British Journal of Radiology. 2016;**89**(1062):20160021

[19] Stone SE, Morris TA. Pulmonary embolism during and after pregnancy. Critical Care Medicine. 2005;**33**:S294-S300

[20] Shaikh N. Heparin-induced thrombocytopenia. Journal of Emergencies, Trauma, and Shock. 2011;**4**:97-102

[21] Aarskog D, Aksnes L, Markestad T, et al. Heparin induced inhibition of 1,25-dihydroxy vitamin D formation. American Journal of Obstetrics and Gynecology. 1984;**148**:1141-1142

[22] Hall JG, Pauli RM, Wilson KM. Maternal and fetal squeal of anticoagulation during pregnancy. The American Journal of Medicine. 1980;**68**:122-140

[23] Ahearn GS, Hadjiliadis D, Govert JA, et al. Massive pulmonary embolism during pregnancy successfully treated with recombinant tissue plasminogen activator. A case report and review of treatment options. Archives of Internal Medicine. 2002;**162**:121-127

[24] Saeed G, Möller M, Neuzner J, Gradaus R, Stein W, Langebrake U, et al. Emergent surgical pulmonary embolectomy in a pregnant woman: Case report and literature review. Texas Heart Institute Journal. 2014;**41**(2):188-194

[25] Levinson G, Shinder SM. Vasopressors in obstetrics. Clinical Anesthesia. 1974;**10**:77-109

[26] Bourjeily G et al. Lancet. 2010;**375**:500-512

Chapter 8

Venous Interventions: From Lower-Limb Deep Vein Thrombosis to May-Thurner Syndrome and Budd-Chiari Syndrome

Ding-Kwo Wu, Chih-Wei Chen, Hao Xu and Maoheng Zu

Abstract

Over the past decade, there have been great innovations in the diagnosis of venous disorder since the introduction of dual-source computed tomography (DSCT) in 2006. It provides fast and reliable diagnosis of deep vein thrombosis (DVT) with the capability of full leveling of thrombus burden and allows early endovascular interventions with pharmacomechanical aspiration thrombectomy (PMAT) being performed aiming to reduce the post-thrombotic syndrome (PTS) and improve quality of life. The newly introduced ultrafast clot removal system, in patients who failed with PMAT, AngioJet, and EKOS, aids in rapid restoration of venous flow and decline of venous hypertension to mitigate the valve damage. Percutaneous transluminal angioplasty (PTA) and stenting yield high technical success rate of 93–96% and a promising short-term 1-year and 2-year patency of around 93% and 75–79%, respectively, for symptomatic May-Thurner syndrome (MTS). Based on the cumulative endovascular treatment experience in over 2000 cases in Xizou, China, some relevant precipitating factors are addressed, and a new classification of subtypes have been proposed to guide the proper selection of endovascular management of Budd-Chiari syndrome (BCS).

Keywords: deep vein thrombosis, computed tomographic venography, magnetic resonance venography, digital subtraction angiography, May-Thurner syndrome, Budd-Chiari syndrome, catheter-directed thrombolysis, pharmacomechanical aspiration thrombectomy, percutaneous transluminal angioplasty, stenting

1. Lower-limb deep vein thrombosis (DVT)

1.1 Introduction and background

It has been estimated that approximately 200,000 to 250,000 cases of lower-limb DVT occurred annually in the USA [1, 2]. Dated back as early as in 1860, German pathologist Rudolf Virchow initially depicted the gold rules of pathophysiology involved in DVT: the triad of (1) venous stasis, (2) endothelial damage, and (3) hypercoagulability. Venous stasis can be resulted from external compression,

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traumatized venous wall injury as a consequence of indwelling catheters and devices, and infusion of chemotherapeutic agent and lipid substance as prescribed in hyperalimentation, as well as in lower cardiac output state and prolonged immobilization. Hypercoagulability is generally linked to hematological and genetic disorders, i.e., polycythemia rubra vera, antithrombin III deficiency, protein S/C deficiency, hyperhomocysteinemia, and cancerous disease, oral contraceptive and tobacco use, as well as pregnancy and postpartum state [3, 4].

2. Clinical presentations

The most common symptoms and signs in acute DVT (<2w) are a tender and swollen lower limb along with local heat on palpation. In subacute (2w–6 m) and chronic (>6 m) DVT, patients usually presented with chronic lower-limb swelling, pigmentation, and ulceration in lower calf and ankle. Among the complications resulted from lower-limb DVT, the most serious one is acute pulmonary embolism, which can precipitate acute pleuritic chest pain, tachycardia, hypotension, hypoxia, and death from acute decompensated right heart failure in those patients presented with massive pulmonary embolism. Despite adequate medication used, post-thrombotic syndrome occurs in approximately 20–40% of patients with subacute and chronic lower-limb DVT [2–4].

3. Diagnostic imaging modalities

A diversity of imaging tools, i.e., ultrasonography with color-flow mapping, CT venography, MR venography, radionuclide venography, and contrast venography, have been implicated in the diagnosis of lower-limb DVT.

3.1 Ultrasonography (US)

Grayscale ultrasonography is the first-line tool, which can delineate low echogenicity or nearly anechoic thrombi and a non-compressible vein in acute DVT, with a sensitivity and specificity of 90–100%, respectively. In chronic DVT, diagnosis can be made on the basis of detecting (1) a thickened vein wall with hyperechoic intraluminal projections, (2) a non-compressible vein, (3) little or no change of vein caliber with flow augmentation, and (4) the presence of collateral vessels. Color-flow Doppler ultrasound can assist in the detection of a patent versus non-patent venous lumen [5, 6]. The limitations of US are the inconsistency in the depiction of below-knee venous thrombi in terms of anatomical variants and small caliber as well as potential difficulty in assessing iliac veins [7].

3.1.1 Contrast venography

Prior to the invention of US, contrast venography, done with cannulation of a sizable pedal vein and a tourniquet compressing at the ankle, on a remote control unit with tilting facility, had been the diagnostic gold standard of lower-limb DVT. However, the foot back tends to be congestive and swollen, and a sizable vein for cannulation may not be available. A couple of methods have been raised to enhance the detectability including limb elevation and Ace wrap, digital compression, nitroglycerin paste, Doppler US localization with a pencil probe, and surgical cutdown. Technical difficulty does exist. In addition, there are certain diagnostic pitfalls and tricks that may result in false-positive and false-negative consequences,

mainly incomplete contrast opacification of the deep venous system and a variety of artifacts that may mimic intraluminal clots [8–10].

In acute DVT, the hallmark features are the detection of filling defects (thrombi) with simulated "tram-tracking sign" appreciated between the venous lumen and the venous wall and the acute venous cutoff identified not at the valve region. The affected veins tend to get distended along with the increased thrombi burdens [3, 9, 10]. In chronic DVT, the hallmark features are (1) clot retraction, (2) clot recanalization, (3) valve destructions, and (4) loss of normal venous pathway. In selective minor case, the affected veins may recanalize completely and appear essentially normal [10].

3.2 Magnetic resonance venography (MRV)

Over the past decade, there have been remarkable advances in the magnetic resonance (MR) imaging technology of deep venous system that prompt both non-contrast-enhanced and contrast-enhanced MRVs nearly as comparable as contrast venography in the diagnostic accuracy of DVT [11–13]. As shown in 2007, one meta-analysis evaluated the diagnostic sensitivity and specificity of MRV in lower-limb DVT to be 92 and 95%, respectively [14]. Aside from claustrophobia, the limitations of MRV include a lengthy procedure time, pregnancy, and patient with renal failure and with implanted metallic devices.

3.3 Computed tomographic venography (CTV)

CTV had been used for diagnosis of DVT at the single-slice CT era [14, 15]. Over the past decade with the emergence of dual-source computed tomography (DSCT) in 2006 by Siemens, tremendous advances in fundamental technology and clinical utility of CTV have been brought about. In our institution, since the availability of the second-generation DSCT (Somatom Definition Flash, Siemens) in September 2009, we were able to develop our own scanning protocol in CTV with superb imaging quality in the majority of the patients around 2013 (**Table 1** and **Figure 1**). Proper opacification of deep venous system of lower limb, starting from the lower inferior vena cava (IVC) down to the mid-level of tibioperoneal veins, can be acquired as a routine (**Figure 2**). Except in some selective patients with idiopathic increase in below-knee peripheral vascular resistance (PVR) and in patients with advanced

1. Anatomic collimation: Aortic bifurcation at L3–L4 level to toes
2. Contrast bolus injection: 120–140 ml of Ultravist 370 mg I/ml BMI: <23.9 120 ml, 24–27.9 130 ml, > 28 140 ml Flow rate: 4 ml/s, followed by a 40 ml saline chasing
3. Scan initiation: 3 min after contrast bolus
4. Scan mode: Flash
5. Scan parameters Acquisition: 128 × 0.6 mm Slice thickness: 5 mm Pitch: 2.5
6. Dose modulation: Care dose 4D
7. Effective radiation dose: 4–5 msv

Table 1.
Dual-source CT venography protocol.

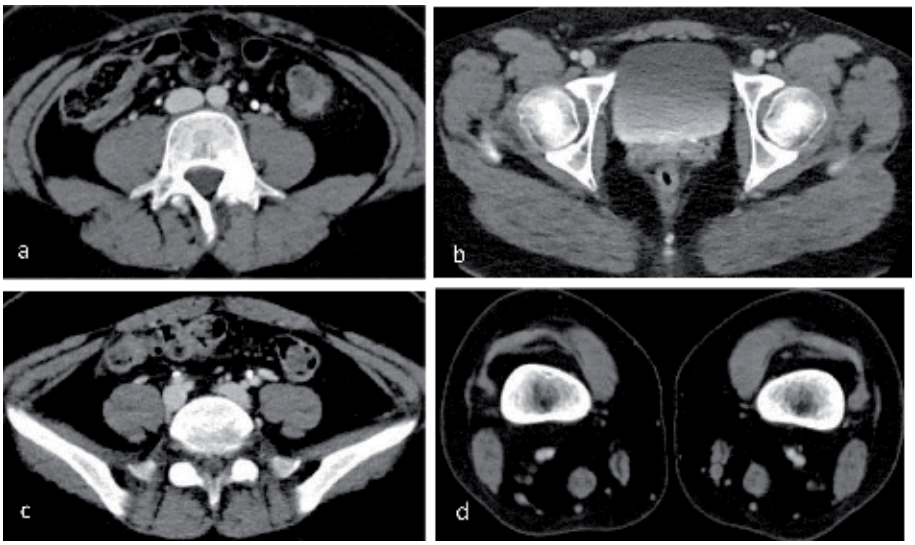

Figure 1.
(a-d) CTV depicted optimal opacification of venous structure from bifurcation of IVC to the lower level of popliteal veins.

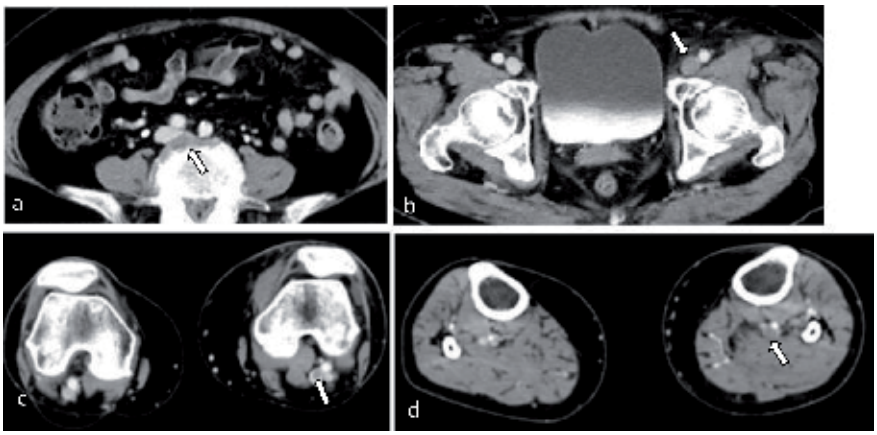

Figure 2.
(a–e) CTV depicted extensive DVT from the LCIV to tibioperoneal veins (arrows).

peripheral arterial obstructive disease (PAOD), both of which result in sluggish input arterial flow and thus suboptimal venous opacification at CTV. In patients suspected of coexisting PAOD, a CT arteriography can be performed in one set prior to proceeding of CTV (**Figure 3**). Approximately 80 ml of 370 mgI contrast medium is injected at rate of 4 ml/s, and the collimation is made at 64 × 0.6 mm to cover shortly above the aortic bifurcation down to the toes. The CTA is displayed in maximum intensity projection (MIP) and bone removal to facilitate visual reading. The tibioperoneal artery greater than 1.5 mm can be well delineated; however, in the lower calf where close alignment of the artery is adjacent to the bone cortex, loss of artery outline may be encountered due to equalization of post-processing threshold.

In a recent meta-analysis focused on the diagnosis of lower-limb DVT, the cumulative sensitivity and specificity are 96 and 95%, respectively [16]. The limitations of CTV are patients with significant renal failure, with idiopathic increase in below-knee PVR, and with severe PAOD.

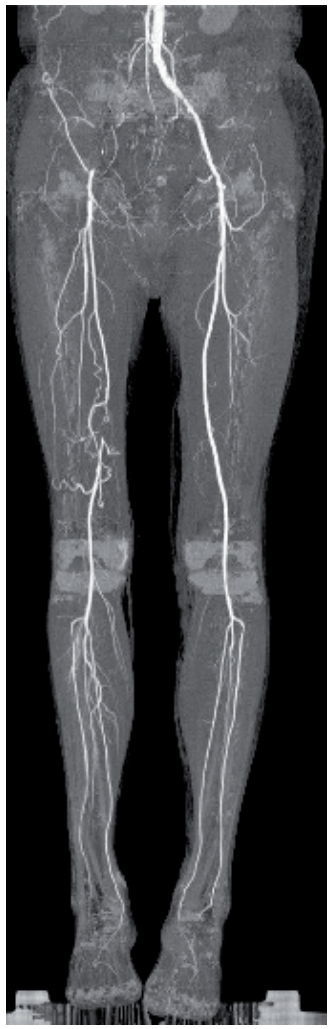

Figure 3.
CT arteriography at the same set as CTV showed high-grade imaging quality as well as identification of two discrete obstructions in the right iliac and superficial femoral arteries. Collateral arteries were also clearly depicted.

4. Indication for endovascular interventions in DVT

4.1 Introduction and background

Anticoagulation therapy has long been the first-line management in patients presented with acute DVT. In the 1980s, systemic thrombolysis using streptokinase demonstrated better resolution of thrombus than heparinization alone but carried an unacceptable risk of bleeding complication [17]. It was until the late 1990s when intraluminal catheter-directed thrombolysis (CDT) was initiated as an adjuvant to treat those patients in whom heparin worked slowly and patient could not tolerate intractable swelling of the affected lower limb. The treatment safety and the clinical efficacy of CDT were validated in iliofemoral DVT by Bjarnason et al. in 1997 [18]. Within the following years, after conducting a nationwide multicenter study, Mewissen et al. proposed that CDT was safe and effective and to be preferentially carried out in proximal iliofemoral and femoropopliteal DVT in patients presented

with symptomatic venous obstruction [19]. In 2006, the Society of Interventional Radiology published the guidelines for the treatment of lower extremity deep vein thrombosis [20]. (1) In a clinical subset of patients objectively documented with iliofemoral DVT, early debulking of thrombus burden can help mitigate post-thrombotic syndrome (PTS). (2) In patients presented with severe symptoms of massive swelling and intractable pain, early intervention helps reduce mobility and prevent progression to venous gangrene (**Table 2**). As the thrombus ages, approximately 10 to 14 days after acute onset, CDT becomes less effective in terms of thrombus debulking. As indicated in the CaVenT study, the incidence of PTS reduced to 14.4%, and the 6-m venous patency rate was 65.9% in CDT vs. 47.4% in control, respectively ($p = 0.012$) [21]. The long-term outcome of the ATTRACT study, a multicenter randomized controlled trial, was published in *The New England Journal of Medicine* in December 2017. The result showed no reduction of overall PTS at 2 years (48.0% vs. 47.4%), but a noteworthy difference of 6% declines in moderate-severe degree of PTS (24% vs. 18%, $p = 0.04$) [22]. Given that primary endpoint was not achieved, however, in selective patients presented with profound DVT symptoms and lower risk of bleeding, the benefit of CDT in reducing moderate-severe PTS and earlier symptomatic relief [23, 24] may gain reappraisal by clinicians and interventional radiologists. In addition, patients presented with significant venous steno-occlusive disease after CDT can be managed concomitantly with percutaneous transluminal angioplasty (PTA) or stent deployment to prevent recurrence of DVT [25].

4.2 Current technology in endovascular managements of DVT

4.2.1 Patient selection

In our institution, patients suspected of having DVT routinely received color-flow mapping and Doppler US and CTV. In advanced symptomatic patients presented with CT documentation of high-level (femoroiliac veins) or extensive involvement beyond popliteal and tibioperoneal veins but with lower risk of bleeding, CDT is conducted with pharmacomechanical thrombolysis with continued infusion of urokinase for 48–96 hours with an aim for early thrombus debulking and rapid symptomatic relief. While those presented with mild to moderate symptom and CTV documented popliteal and/or tibioperoneal DVTs, conventional anticoagulation is justified.

4.2.2 Access site of CDT

Typically, with the patient in prone position, the popliteal vein of the affected limb is accessed with US guidance. A 3-F micropuncture set (Cook Corporation, Indiana, USA) is used for a safe puncture and access into the popliteal vein as well as to prevent subsequent focal bleeding. The cannula is replaced with a 9-F introducing sheath for easy venous access.

1. Percutaneous aspiration thrombectomy
2. Percutaneous pharmacomechanical thrombectomy
3. AngioJet (rheolysis)
4. Device-assisted thrombolysis Balloon-assisted system Ultrasound-assisted system (EKOS)

Table 2.
Methods of endovascular interventions for deep vein thrombosis.

4.2.3 CDT with pharmacomechanical aspiration thrombectomy (PMAT)

A 5-F pigtail catheter was inserted through the sheath, which is moved up and down a couple of times through the thrombosed segment in popliteofemoroiliac veins, accompanied with simultaneous infusion of 100,000–250,000 IU of urokinase, to assist macerating the thrombus burden for 15 min. An 8-F 60-cm-long multipurpose guiding catheter, attached with a 50-ml syringe, is used to aspirate the macerated thrombi (**Figure 4**). In the case presented with significant residual thrombi, a multi-slit infusion catheter of suitable length (Fountain infusion catheter, Merit, USA) was embedded into the distal-most segment and spared the proximal-most segment for sustained continual infusion of 500,000–1,000,000 IU of urokinase per 24 hours for up to 48–96 hours. The patient is kept in a ACU/ICU for close monitoring of general condition and bleeding. Concomitant intravenous infusion of heparin 20,000 IU per 24 hours to prevent new thrombus formation around the infusion catheter was also deemed necessary. Daily check of aPTT (<1.5 time of control level) and fibrinogen and platelet count was mandatory. The patient is sent back to DSA suite every 8–12 hours to check for the resolution of thrombi and repositioning of infusion catheter to facilitate further thrombus resolution toward the proximal end until satisfactory results are achieved. The infusion dose of urokinase can be adjusted depending on the bulk of residual thrombi. After successful CDT, the patient is put on anticoagulation with warfarin for at least 6–12 months.

4.2.4 CDT with new devices by using pharmacomechanical catheter-directed thrombolysis

The consensus that the earlier the thrombi lysed, the less severe the PTS will be paves the way for a better quality of life and less daily limitation of physical activity. Speedy thrombus resolution to salvage valve damage and venous insufficiency sounds reasonable and practical. In recent years, an ultrasound-emitting thrombolytic infusion catheter (EKOS Corporation, Bothell, WA) and the AngioJet Rheolytic Catheter System (MEDRAD Interventional, Minneapolis, MN) have become available in our institution (**Table 2**). In terms of being high-cost treatment modalities, they both are reserved for those patients who failed to respond well with PMAT (**Figures 5** and **6**).

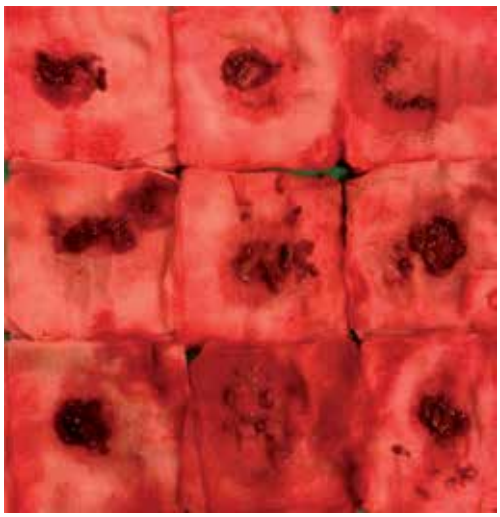

Figure 4.
Relatively fresh and subacute thrombi were aspirated by PMAT from the left iliofemoral veins in a 32-year-old female taking oral contraceptive pills for dysmenorrhea.

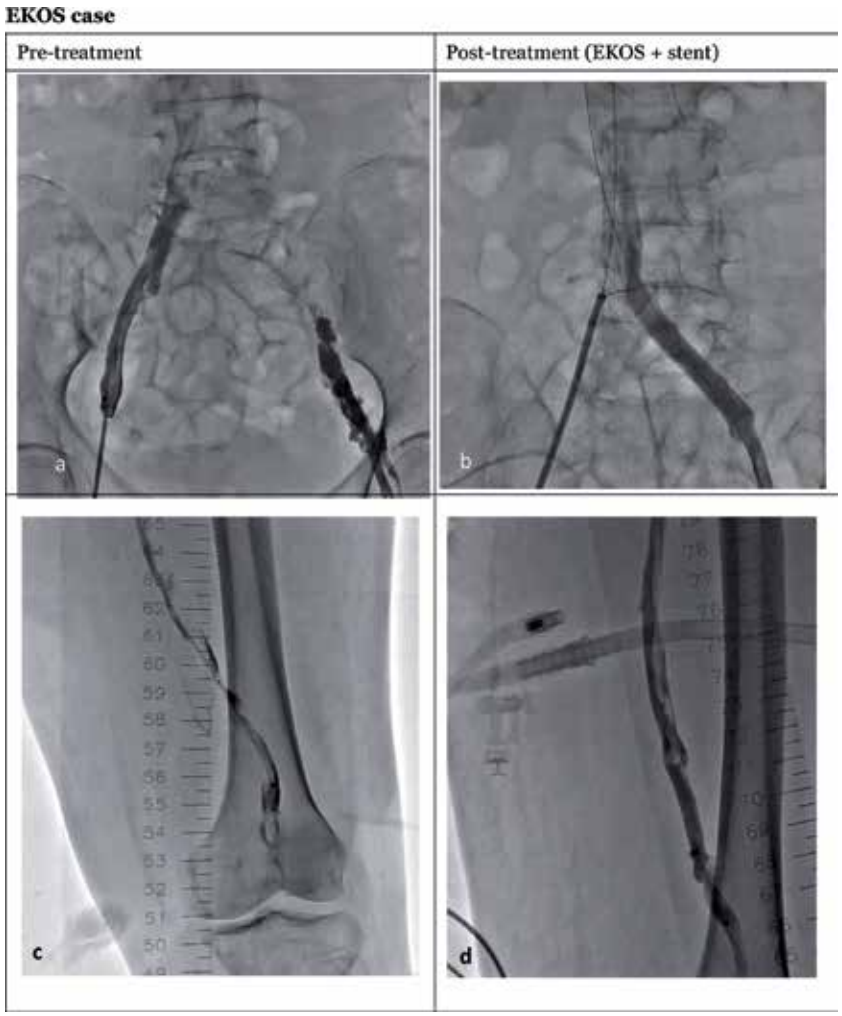

Figure 5.
An 81-year-old female with lower third esophagus adenocarcinoma, cT3N0Mb, Stage III under palliative chemotherapy, suffered from left leg swelling, and CTV documented massive DVT in iliofemoropopliteal veins. (a and c) Nearly complete obstruction of left iliofemoropopliteal veins by DVT. (b and d) s/p EKOS catheter for enhanced CDT treatment and s/p PTA and Wallstent deployment in left common and external iliac vein restored good blood flow.

4.2.5 Percutaneous transluminal angioplasty and stenting

After successful PMAT is achieved, the whole affected proximal venous pathway should be documented with DSA for any residual steno-occlusive disorder. A 0.035″ hydrophilic guide wire (Terumo, Tokyo Japan) is negotiated, and a 4-F Teflon-coated catheter (Terumo, Tokyo Japan) is advanced through the lesion. A 0.035″ stiff hydrophilic guide wire (Terumo, Tokyo Japan) is exchanged. Sequential ballooning was conducted, with 3-mm, 5-mm, and 8-mm balloons until the balloon waist was completely gone, to accommodate a self-expandable stent of sufficient size and length, mainly the Wallstent (Boston Scientific, Massachusetts, USA). Postdeployment dilation is carried out with a balloon catheter of appropriate size to scaffold the venous fibrosis that frequently comes across with significant venous stenosis. Follow-up DSA is performed to document the technical success, which is graded as a residual stenosis of <30% [26, 27] (**Figure 7**). Aspirin 100 mg and clopidogrel 75 mg are recommended for at least 3 months after stenting.

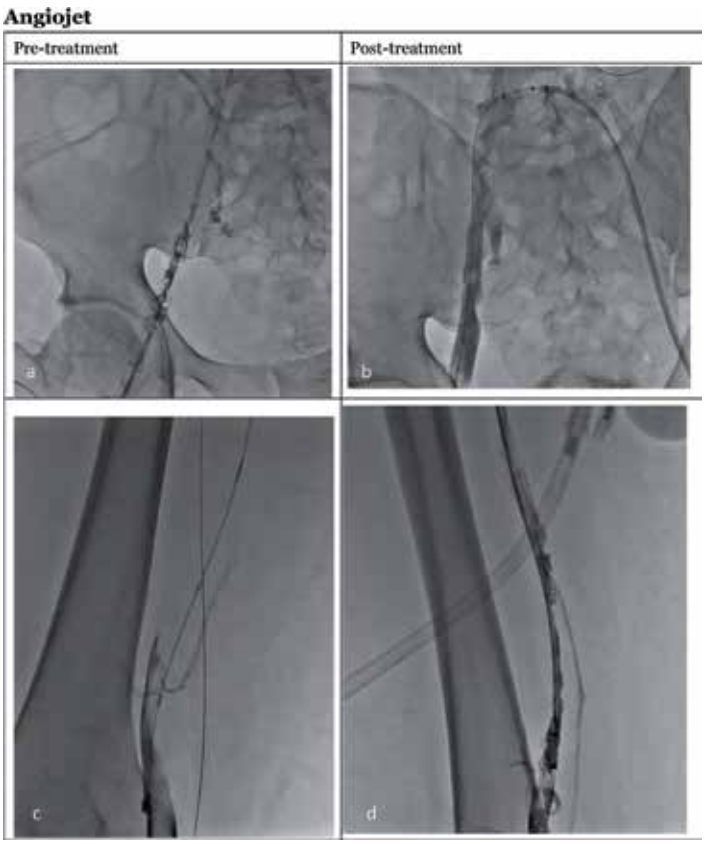

Figure 6.
A 31-year-old obese male with hypertension suffered from gunshot wound over the abdomen and complicated with diffuse right leg iliofemoral DVT. (a and c) Diffuse DVT in the right iliofemoropopliteal veins due to immobilization. (b and d) After AngioJet, good blood flow regained.

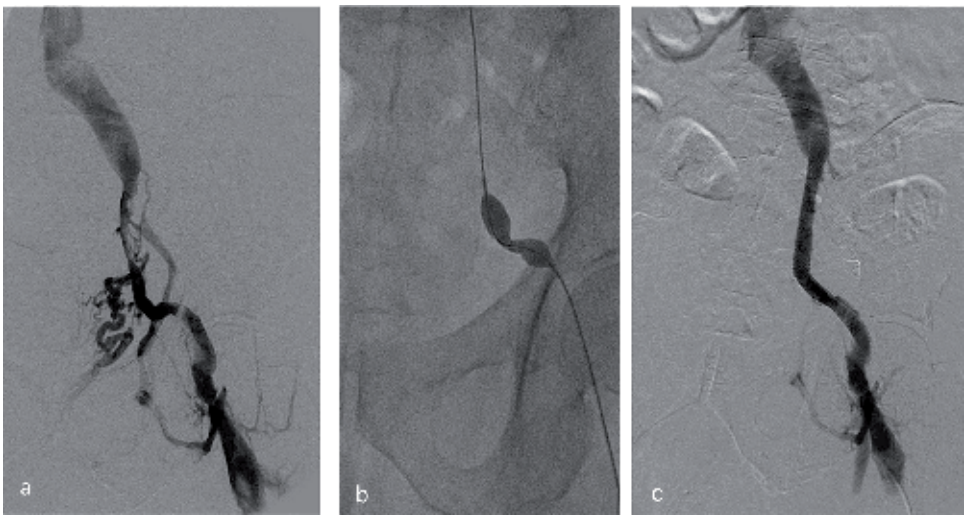

Figure 7.
A 48-year-old male developed chronic DVT in the left iliofemoral veins as a complication of dwelling perm catheter and successfully managed with PTA and two overlapping 8 m and 10 cm Wallstents. At 8-year follow-up, the stents remained patent. (a) Contrast venography revealed long-segment stenosis of the left iliofemoral veins and venous collaterals. (b) Balloon waist at predilation with an 8-mm balloon catheter. (c) Immediately after stenting, good flow is restored and minimal venous collaterals visualized.

5. Endovascular management of May-Thurner syndrome (MTS)

5.1 Introduction and anatomical background

MTS has two synonyms: Cockett syndrome and iliac vein compression syndrome. In 1983, Dr. Ernest Ferris for the first time proposed May-Thurner syndrome in memory of Dr. May and Dr. Thurner for their relevant contributions [28]. The first description of a septum-like structure in the left common iliac vein (LCIV) was made in 32% (10 out of 32) of cadavers, in 1906 by an anatomist McMurrich, with which a congenital remnant was implicated as such [29]. In 1943, Ehrich and Krumbhaar through anatomic dissection in 412 cadavers found that obstructive lesion in the left common iliac vein (LCIV) in 23.8 and 33.8% of the lesion occurred after the first decade. The lesions were regarded as acquired and not congenital. In 1957, May and Thurner, through autopsy in 430 cadavers, demonstrated that among 19% of cadavers, the overriding right common iliac artery (RCIA) compressed the LCIV against the spine [30]. Other investigators also presented different incidence of spurs in the LCIV by different imaging tools: 14% by Negus et al. [31], 50% by Vollman et al. with vascular endoscopy [32], and 62% by Juhan et al. with contrast venography [33], respectively.

5.2 Pathophysiology of MTS

Long-lasting pulsatile injury elaborated by the overlying RCIA prompted projectile fibrotic spurs into the lumen of the LCIV, which in turn resulted in accumulation of elastin and collagen over the spurs and extensive intimal proliferation of venous wall. Three varieties of classic venous spurs had been addressed, especially associated with a lower bifurcation position of the abdominal aorta [29]. Other theories had been implicated as possible causative factors, namely, compression by pregnant uterus [34] and by sigmoid colon associated with constipation [35]. Currently, with availability of modernized cross-sectional imaging modalities, like intravascular ultrasound and optic coherence tomography, the venous spurs can be well depicted and precisely documented the severity of venous obstruction than contrast venography [36–38]. Regardless of spur-forming mechanism [36], congenital or acquired, in case predisposed to hypercoagulability, thrombosis of the LCIV then issues initially at the stenosed segment and propagates in antegrade and retrograde fashions. However, in chronic MTS, the patient may be asymptomatic for quite a certain period of time if sufficient venous collaterals have developed [39].

5.3 Clinical manifestation and staging

MTS has a strong tendency to affect young and middle-aged woman (mean age, 42 y/o), although it does affect man [40]. In acute stage, the majority of patients frequently presented with sudden onset of pain and swelling of the left lower extremity due to the accompanying DVT. In chronic stage, the symptoms may be more or less vague to define but generally comprised of persistent edema, heaviness, lower calf and ankle skin pigmentation, venous claudication, and ulcer as well as varicose veins [41, 42]. Rarely, in some selective patients affected with phlegmasia alba dolens and phlegmasia rubra dolens, limb salvage may provide an extremely difficult challenge for the multidisciplinary team physicians. Based on the clinical and imaging findings, MTS is classified into three stages: Stage I, asymptomatic LCIV compression; Stage II, presence of intraluminal venous spurs; and Stage III, occurrence of DVT in the LCIV (**Figure 8**) [43, 44]. Failure to correct

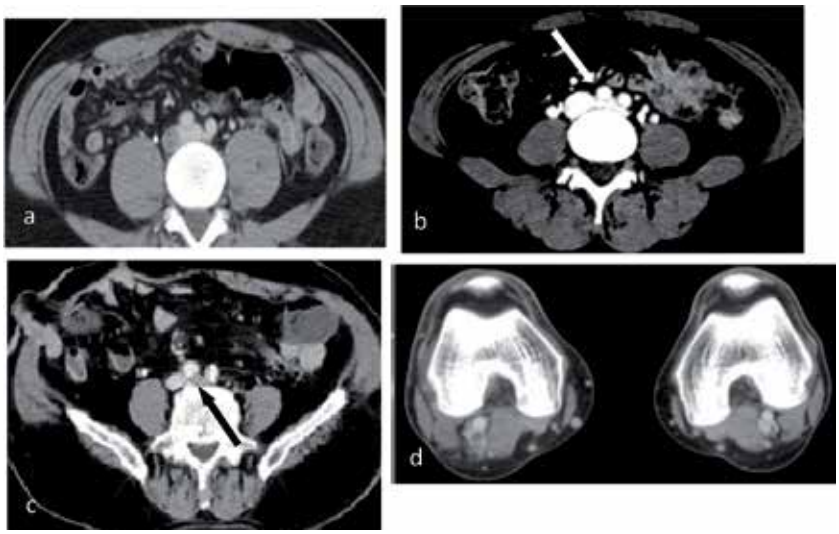

Figure 8.
Classification of MTS into three clinical stages. (a) CTV showed Stage I MTS 9 (arrow) incidentally while imaging of DVT. (b) CTV showed Stage II MTS presented with venous spur. (c and d) CTV showed Stage III MTS presented with DVT (black arrow).

the underlying anatomic substrate of the LCIV, complication of MTS can include pulmonary embolism, chronic venous stasis, PTS, and iliac vein rupture [39].

5.4 Diagnostic imaging modalities of MTS

As mentioned in the imaging diagnosis of DVT, a variety of imaging tools can offer a figure of diagnostic sensitivity and specificity. Each has its own advantages, disadvantages, and limitations. Among them, US is the first-line followed by CTV, MRV, and contrast venography to objectively document the level of DVT and grade the severity of iliac vein obstruction. A stenosis of >50% in the LCIV is considered as hemodynamically significant. As the stenosis percentage of the LCIV may be periodically altered with the circulating blood volume and the body position [38, 39], in suspicious case, a pressure gradient across the RCIV and LCIV of >2 mmHg at rest and > 3 mmHg with exercise aids in making a definite diagnosis. Over the past decade with the availability of second generation of DSCT scanner (Somatom Definition Flash, Siemens) in our institution, CTV has nearly replaced others and become the first-line imaging modality for MTS in terms of rapid dataset acquisition and precise leveling of steno-occlusion of the LCIV and the associated DVT [45–47]. In conjunction with 3-D volume rendering technique at CTA, the compressed segment of the LCIV by the overlying RCIA can be appreciated more precisely than contrast venography. Of paramount importance is the precise depiction of floating thrombi in the lower segment of the IVC with CTV, which may prompt the strategy to implant a temporary IVC filter to prevent pulmonary embolism during endovascular procedure.

5.5 Endovascular treatment of MTS

The endovascular treatment of MTS by PTA and stenting has been reported in the literature to be minimally invasive, technically feasible, and safe and clinically effective. Isolated PTA is not effective, similar to the result in other large central veins. The access site is from the left popliteal or common femoral veins.

5.5.1 Percutaneous CDT in the treatment of MTS with extensive DVT

Pharmacomechanical aspiration thrombectomy (PMAT), as described in the treatment of isolated DVT, is well suited for MTS in acute stage presented with extensive thrombi, which is thoroughly dictated in Subsection 4.2.3.

5.5.2 Percutaneous transluminal angioplasty (PTA) and stenting for MTS

In patients with isolated stenosis but free of DVT, PTA and stenting are a straightforward procedure. In 1995, Berger et al. reported the first successfully

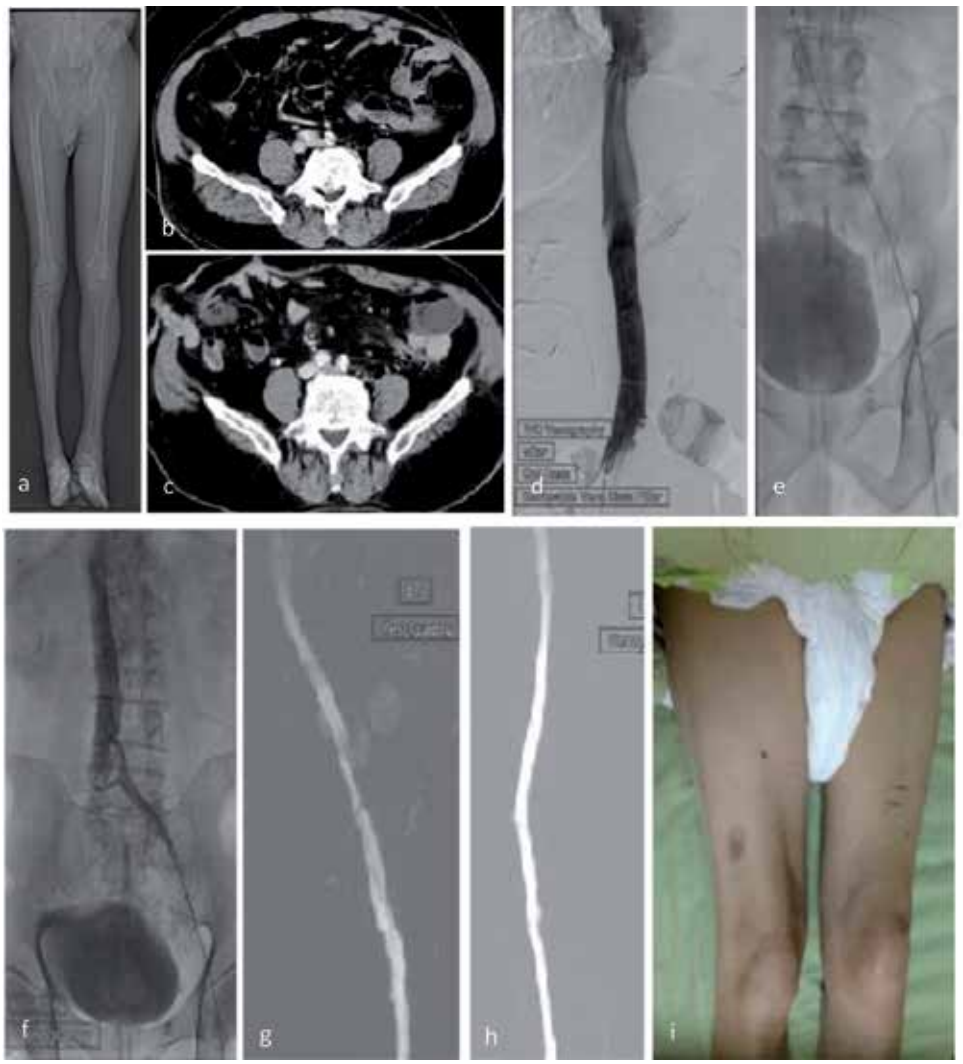

Figure 9.
A 70-year-old male with Stage III MTS successfully treated with PTA and stenting. (a) CT topography showed remarkable swelling of the entire left lower extremity. (b) CTV incidentally showed Stage II MTS half year age at workup for colon cancer. (c) CTV showed Stage III MTS with diffuse DVT from the upper left tibioperoneal vein to the common iliac vein. (d) Contrast venography showed minimal floating thrombin into the IVC (arrow). (e) A Teflon-coated 4-F catheter successfully navigated through the tight stenosis in the common iliac vein (arrow). (f) After sequential PTAs, a minimal channel was reanalyzed in the LCIV. (g and h) After a 14 mm x 80 mm Wallstent deployment and thrombolysis with a multi-slit infusion catheter for 48 hours, successful recanalization was achieved. (i) At discharge (8 days after admission), the left leg limb was even smaller than the right leg.

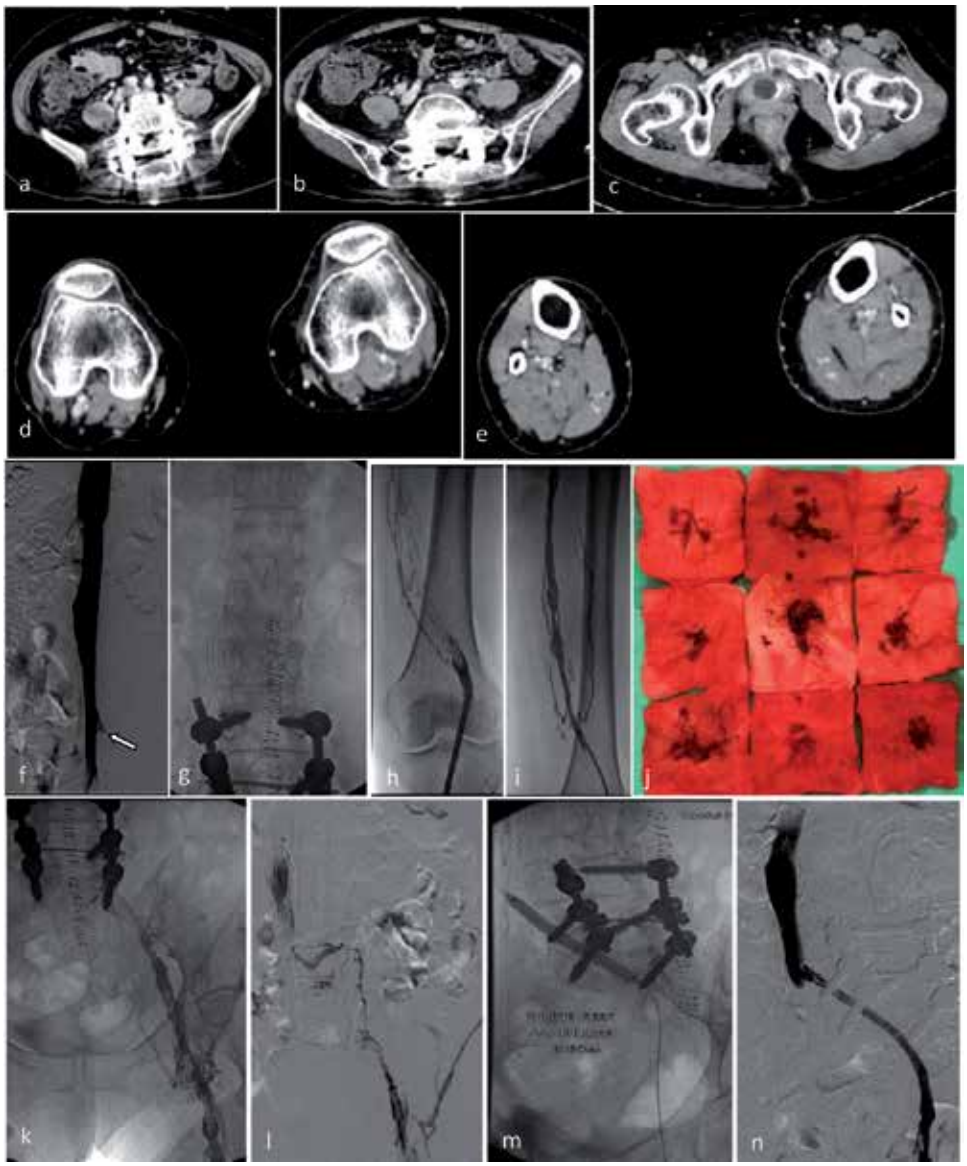

Figure 10.
A 65-year-old schizophrenic female suffered from subacute Stage III MTS, successfully recanalized with PMAT and Wallstent deployment. (a–e) CTV showed excellent depiction of massive DVT spanning from the lower IVC down to the left tibioperoneal vein. (f and g) Venography demonstrated floating thrombi in the lower IVC (arrow), and an Optease caval filter was implanted to prevent pulmonary embolism. (h–j) Subacute thrombi were removed with aspiration thrombectomy. (k and l) After aspiration thrombectomy, venography revealed minimal residual thrombi and long-segment tight steno-occlusion of left iliofemoral veins and venous collateral. (m and n) After sequential PTAs and Wallstent deployment, the venous flow was restored, and at 2.5-year follow-up, the stent remained patent.

deployed stent to decompress left iliac vein obstruction. After successful PMAT is achieved, as done exactly in the treatment of DVT section, a 0.035″ hydrophilic guide wire (Terumo, Tokyo Japan) is vigorously negotiated through the steno-occlusion in the LCIV, and a 4-F Teflon-coated catheter (Terumo, Tokyo Japan) is advanced in to the lower IVC. A 0.035″ stiff hydrophilic guide wire (Terumo, Tokyo Japan) is exchanged. Sequential ballooning was conducted, with 3-mm, 5-mm, and 8-mm balloons until the balloon waist is completely gone, to accommodate a self-expandable stent of sufficient size and length. Wallstents (Boston

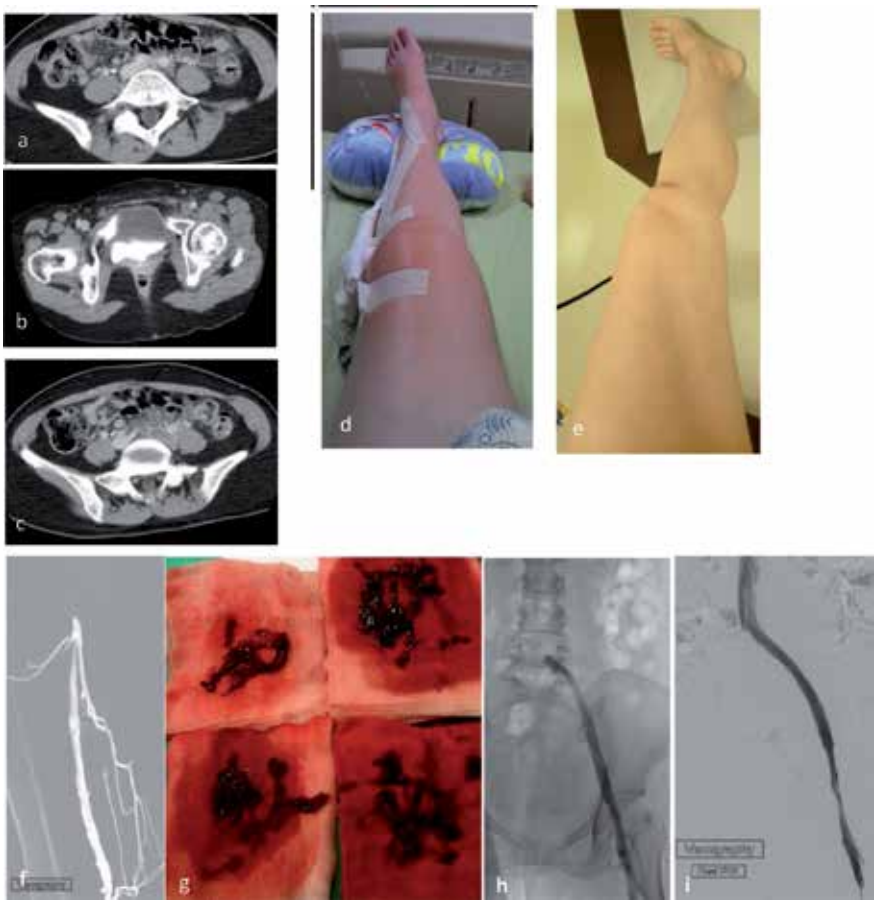

Figure 11.
A 41-year-old with MTS Stage III presented in acute stage was successfully managed with PMAT, PTA, and stenting. (a–c) CTV depicted extensive DVT in the left femoroiliac veins. (b) Pre-treatment photo showed swelling of the left leg and cellulitis. (e) Posttreatment photo showed disappearance of swelling and healing of cellulitis at 1-month follow-up. (f and g) Venography showed extensive DVT above the left femoral vein and relatively fresh thrombi obtained by PMAT. (h and i) After PTA and stenting in the LCIV, good patency was depicted, and minimal residual thrombi were treated with warfarin.

Scientific, Massachusetts, USA) of 12–14 mm in diameter and 80–120 mm in length are used to span the lesion. During the deployment, the Wallstent is initially deployed in the lower IVC, after which the whole unit is pulled down to retain a distal landing zone in IVC of approximately 1–1.5 cm and spans over the entire steno-occlusive segment with a proximal landing zone of >2 cm. Postdeployment dilation is carried out with a balloon catheter of appropriate size to scaffold the venous spurs and fibrosis that frequently accompany MTS. Follow-up DSA is performed to document the technical success, which is graded as a residual stenosis of <30% (**Figures 9–11**) [26, 27]. Aspirin 100 mg and clopidogrel 75 mg are recommended for at least 3 months after stenting. Kaplan-Meier life table analysis is used to calculate the primary and secondary patency rate in the follow-up periods. Repeat PTA/stenting as indicated is relevant to maintain the long-term patency.

5.5.3 Technical success and treatment outcome of MTS

As reported in the literature, the technical success rates ranged between 93 and 96% [42–44, 47]. With repeat PTA/stenting, the midterm patency rates were

promising and ranged between 95 and 100% [47, 48]. Although the prevalence of overall PTS did not decline with the adjunct use of PMAT, however, the reduction of moderate to severe degree of PTS was noteworthy. As to the long-term patency, it reserves meticulous monitoring.

6. Budd-Chiari syndrome

Budd-Chiari syndrome (BCS) occurs when obstruction of the hepatic venules anywhere along the inferior vena cava (IVC) to the right atrium junction can lead to portal hypertension. BCS can be life-threatening. The prevalence of BCS has different geographic variances. In Western countries, the prevalence of BCS is rare, occurring in about 1 in every 2.5 million people, whereas in some Asian countries, such as China, India, and Nepal, BCS is a common disease. For instance, in China's Yellow River and Huaihe River region, 6.8–12 people per 100,000 people suffer from BCS; and more than 20,000 BCS have been documented in China [49]. Differences in obstruction sites can also be seen between Western and Asian populations. In the West, hepatic vein occlusion is more common, and venous congestion involving the IVC is less documented. However, in Asia, the diaphragm-type Budd-Chiari syndrome accounts for as high as 70% of all cases. Geographical variance, obstruction location, and pathological and anatomical differences have led to significant differences in clinical symptoms, treatments, and prognosis of BCS in the East and West. The development of modern imaging has enabled observing the hepatic vein, portal vein, inferior vena cava, and azygous vein in vivo, which revealed discordances in comparison to traditional liver biopsy and autopsy findings as described in the previous literature. Therefore, it is necessary to revisit BCS.

6.1 Etiology

BCS is considered primary or secondary based on the origin of the hepatic venous outflow obstruction. When the hepatic vein outflow tract is compressed or infiltrated, it is regarded as secondary BCS. Some examples include a primary or metastatic tumor of the liver, leiomyomas of the inferior vena cava, and tumor thrombus. So far, the most common etiology of primary BCS in Western countries is thrombosis, and 25–46% of patients are in prethrombotic or hypercoagulable states. Therefore, primary BCS is predisposed by prethrombotic conditions [50]. However, in China, the etiology of BCS is different. The current research shows that in China, the primary thrombotic disease is not a common cause of BCS. Studies have demonstrated that (1) patients with inferior vena cava obstruction have elevated blood vascular endothelial growth factor (VEGF) [51], (2) there is higher groundwater iodine concentration in high-prevalence areas [52], (3) BCS patients have higher blood and urine iodine concentrations [53], (4) people living in rural areas have a higher prevalence, (5) restenosis can occur despite balloon venoplasty of the hepatic vein and inferior vena cava [54], and (6) membranous reformation can occur despite surgery.

Statistical analysis of 2406 patients found that the proportion of hepatic vein occlusion in adolescents under 30 years of age was significantly higher than in patients over 30 years of age [55, 56]. The proportion of inferior vena cava obstruction increases with increasing age in patients aged 30–79 years old. In 256 BCS patients in the 60–69 age group, 222 cases have inferior vena cava obstruction, and 34 cases have hepatic vein obstruction (7.2%); only 1 case of 34 cases of BCS in 70–79 years old was hepatic vein obstruction type (2.9%).

6.1.1 Iodine and vascular endothelial proliferation

Guo et al. found that in the groundwater iodine concentration of drinking water in 128 patients with inferior vena cava obstruction in Heze, Shandong Province, 98.44% of the 128 patients had iodine content of 150 μg/l or more, of which 150–300 μg/l accounted for 27.35% and 300 μg/l accounted for 71.09%. This result indicates that an area with high groundwater iodine concentration is at high risk of developing BCS [52]. Further studies by Zhuang et al. found that blood iodine levels in 233 BCS patients were also higher than that in the healthy population [53] (see **Table 3**).

The results showed that the serum iodine concentration of BCS patients was more than five times higher than that of the control group. On this basis, we tested the urine iodine of BCS patients and found that the urinary iodine of BCS patients was also higher than the average population. Li et al. carried out in vitro research on the culture of umbilical vein endothelial cells and fibroblasts using different concentrations of iodide culture medium. It was found that at iodine concentration of 300–500 μg/l, the proliferation of vascular endothelial cells and hyperplasia of fibroblasts can be induced. It is speculated that high iodine concentration can lead to vascular endothelial cell proliferation [57, 58]. Our study of the inferior vena cava septum revealed that the vascular endothelium of the inferior vena cava gradually thickened and merged into a septum. The structure of the septum was fibrous connective tissue in the middle, and the upper and lower layers were vascular endothelium (**Figure 12**). However, the mechanism of how vascular endothelial cells migrate to form inferior vena cava septum is still unclear.

Group	n	Serum iodine (μg/l)	Ranges (min-max)
IVC-type BCS	144	347 ± 272.3[a]	4.3–1095.1
HV-type BSS	71	237 ± 231.1[a]	12.3–937.2
MIX-type BCS	18	307 ± 134.4[a]	72.1–512.7
Control group	60	76.3 ± 25.7	30.2–97.4

Values are given as means±SD.
[a]Versus control group ($p < 0.05$)

Table 3.
Serum iodine levels in patients with BCS in different types and in the control group.

6.1.2 Vascular endothelial growth factor (VEGF)

In studies using enzyme-linked immunosorbent essay of 40 patients with inferior vena cava obstruction, Han et al. revealed that patients with inferior vena

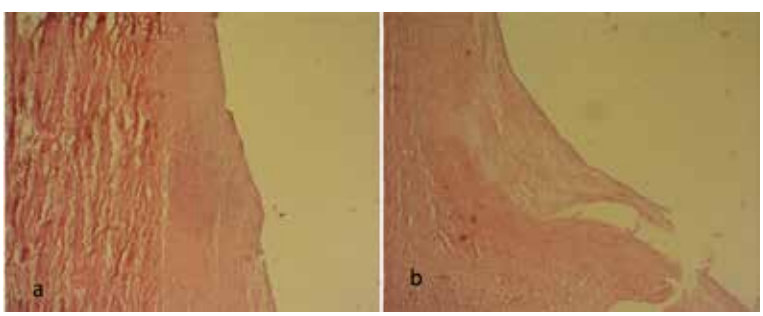

Figure 12.
Thickening of the vascular endothelium above the inferior vena cava septum (a). Lateral migration of thickened vascular endothelium cells and fibrous connective tissue forming the septum (b).

cava obstruction have serum VEGF concentration four times higher than that of the control group. These findings hint that the formation of the IVC septum may be related to inferior vena cava endothelial damage and repair [51] (see **Table 4**).

6.1.3 Abnormal bone marrow hyperplasia and gene mutation

A significant advance in myeloproliferative neoplasm research was the discovery of the Janus kinase 2 (JAK2) V617F mutation in 2005. This mutation was detected in 90% of patients with polycythemia vera and 50% of patients with essential thrombocytopenia and primary myelofibrosis. JAK2 is a member of the Janus family of tyrosine kinases. A retrospective analysis by Kiladjian showed that the detection of the JAK2 V617F mutation was the first diagnostic step in the diagnosis of BCS basic research [59].

In China, Wang collected 65 cases of BCS blood samples from October 2009 to July 2010. EDTA-K2 anticoagulation treatment, DNA extraction, primer design, the establishment of allele-specific polymerase chain reaction system, and comparison of point mutations at nine sites between the study group and control group were performed. After allele-specific PCR, there were nine positive mutations in the study group JAK2 V617F with a mutation rate of 13.85% (9/65). The control group did not have this point mutation. The mutation rate of JAK2 V617F was significantly lower than that of BCS patients in Western countries. The results show that differences exist in the pathogenesis of Chinese BCS compared with that of Western countries [60].

6.1.4 Acquired condition

Many acquired conditions can provoke the occurrence of BCS. Acquired prethrombotic lesions such as Behcet's disease, antiphospholipid syndrome, hyperhomocysteinemia, and paroxysmal nocturnal hemoglobinuria (PNH) promote BCS development. Behcet's disease, paroxysmal nocturnal hemoglobinuria, and oral contraceptives accounted for less than 1% of the study population.

6.2 Clinical manifestation and diagnosis

The clinical manifestations of portal hypertension caused by venous obstruction and posthepatitic cirrhosis and drug-induced (*Gynura segetum*) hepatitis are very similar, which often lead to misdiagnosis. For patients developing abdominal distension, hepatosplenomegaly, massive and refractory ascites, gastrointestinal bleeding, and hypersplenism leading to symptoms of white blood cells and thrombocytopenia, but without past medical history of hepatitis, chronic alcoholism, nor a history of taking *Gynura segetum*, hepatic venous occlusion should be considered. The clinical manifestations of inferior vena cava occlusion have characteristic signs including swelling, hyperpigmentation, varicose veins, and long-term unhealed ulcers of bilateral lower extremities. In addition, bulging varicose veins above the skins of the chest and abdomen wall, longitudinal varicose veins, and the lower back varicose veins are also indicative of inferior vena cava occlusion (**Figure 13a–f**). Non-specific clinical

Group	Number	Average VEGF concentration (ng/ml)	Standard error	t-value	p-value
Control group	40	23.15	19.27	5.273	$p < 0.001$
Study group	40	5.63	8.38		

Table 4.
VEGF concentration value t-test result.

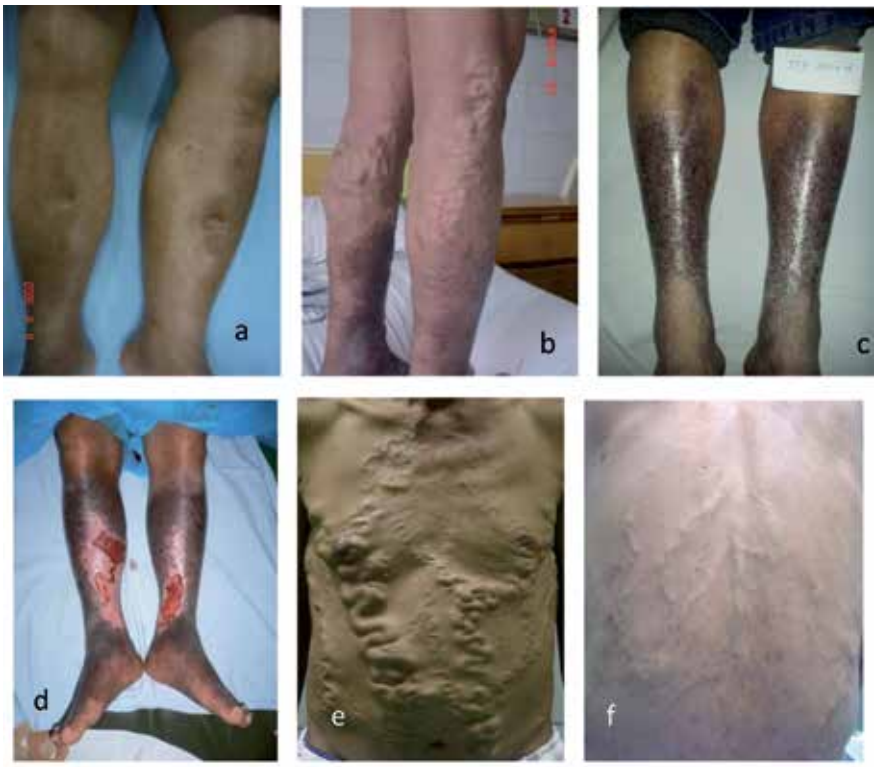

Figure 13.
Clinical manifestations. (a) Swelling of the lower extremities. (b) Varicose veins of the lower extremities. (c) Pigmentation of the lower extremities. (d) Ulcers of bilateral lower extremities. (e) Thoracic and abdominal wall varices. (f) Lumbar dorsal varices.

manifestations of inferior vena cava obstruction include fatigue, exercise-induced asthma, irregular menstruation in women, habitual abortion, and primary infertility.

6.3 Imaging diagnosis

The diagnosis of BCS is based on the manifestations of hepatic venous outflow obstruction. This obstruction can be accurately displayed by noninvasive imaging such as Doppler ultrasound, CT, or magnetic resonance imaging (MRI). Doppler ultrasound is considered to be the preferred initial technique, with the ability to directly show the obstruction and reverse blood flow of the hepatic vein and inferior vena cava. The formation of collateral branches between hepatic veins is an indirect sign of hepatic vein obstruction. Ultrasound has a high sensitivity and specificity for the diagnosis of BCS.

CT scan and MRI are effective methods for diagnosing obstruction of the hepatic vein outflow tract. MR angiography is superior to CT, ultrasound, and angiography in demonstrating anatomic structures of the hepatic veins, accessory hepatic veins (AHV), inferior vena cava, azygous veins, and superficial veins of the abdominal wall (**Figure 14a**). Magnetic resonance angiography can directly display the hepatic veins, the inferior vena cava septum and its thickness, length of segmental occlusion of the inferior vena cava and hepatic vein, location and size of thrombus, as well as the location, orientation, thickness, and number of collateral circulations. Although it is not as effective as Doppler ultrasound in recording the intrahepatic collateral branches, it is unique in showing the extrahepatic collateral and collateral circulations in the abdominal cavity and the abdominal wall (**Figure 14b**). MRI and CT

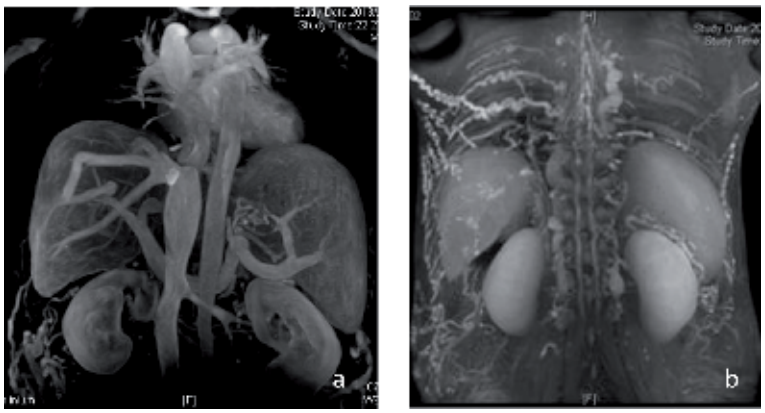

Figure 14.
MRV images. (a) MRV directly shows the hepatic vein, inferior vena cava, and portal vein. (b) MRV shows extensive extrahepatic collateral circulations after inferior vena cava obstruction.

can effectively show areas of liver parenchyma with reduced perfusion or necrosis. Magnetic resonance angiography not only makes the diagnosis of BCS more reliable but also facilitates the planning of treatment strategies. BCS can be precisely diagnosed by magnetic resonance angiography alone [61]; traditional percutaneous biopsy diagnosis of BCS may no longer be necessary [50].

Angiography is still the golden standard for the diagnosis of BCS. It complements ultrasound, CT, and MRI to provide comprehensive imaging diagnosis of BCS. At present, angiography is no longer used exclusively for diagnosis but also as a means of evaluating the efficacy of interventional therapy.

6.4 Definition of a membrane and segmental obstruction

Inferior vena cava and hepatic venous septum formation is a unique pathological feature of BCS. Segmental obstruction can coexist in the inferior vena cava and hepatic vein in some circumstances, making pathological differentiation of the septum and segmentation difficult sometimes. Thus, proper differentiation of the septum and segmentation not only contribute to unified diagnostic criteria and straightforward description of multiple imaging inspection techniques but also promote subtyping BCS. Furthermore, it has significant clinical value for interventional therapy. Therefore, it is necessary to define the inferior vena cava and hepatic venous septum and segmental obstruction.

In January 2016, we organized interventional radiology, pathology, and imaging diagnostic experts to analyze and discuss ultrasound, CT, MRI, and DSA images of more than 1000 patients with BCS and proposed the following viewpoints: inferior vena cava and hepatic vein "septum" and "segmentation" are defined by its thickness, 5 mm or less as a membrane, 10 mm or more as a segment, and 6–9 mm as a transitional zone where the two differentiations can coexist [62].

6.5 Classification and subtype

Because the method of interventional therapy is utterly different from surgical treatment, the classification used for surgery is not suitable for interventional therapy. Imaging diagnosis of hepatic vein and inferior vena cava obstruction has become a routine. After summarizing and reviewing the clinical experience of 10,000 cases of interventional therapy in China, the conditions for the

establishment of BCS interventional classification have matured. Interventional classification will promote and standardize the behavior and procedures of BCS imaging diagnosis and interventional therapy. It has an objective, realistic, and long-term clinical significance.

In 2010, more than 10 experts in the Chinese Interventional Radiology Group engaged in developing an expert consensus guideline on interventional therapy of BCS. BCS is classified into three main types, namely, hepatic vein obstruction type, inferior vena cava obstruction type, and mixed type [63, 64], which are still widely used today. Because of the vast differences in the extent, number, and thrombosis of hepatic veins and the inferior vena cava between individuals, it is necessary to subtype BCS.

In January 2016, experts from the Intracavitary Catheterization Committee of the Chinese Medical Association and experts of interventional radiology, vascular surgery, pathology, and imaging diagnostics discussed to further divide the 3 major types of BCS into 10 subtypes (**Table 5**, **Figures 15–24**). For the first time, the hepatic vein and inferior vena cava obstruction combined with thrombosis were included in the subtype, before which none of the previous classifications have done so.

6.6 Subtyping of BCS as a guideline for endovascular therapy

Endovascular therapies for BCS include percutaneous balloon dilatation, stent implantation, thrombolysis, transjugular intrahepatic portosystemic shunt (TIPS), and hepatic vein reconstruction [65]. Approximately 98% of BCS patients benefit from interventional therapy. The difficulty of BCS intervention varies individually, depending on the procedures performed. Interventional treatment of inferior vena cava septum with a small opening is fairly simple. After completion of inferior vena cava angiography, dilation with a balloon of suitable diameter and length can be done straightforward. However, interventions involving inferior vena cava segmental occlusion, thrombosis formation, occlusion end with the formation of collateral branches, or diffuse hepatic vein occlusion can take the operators hours or even days to complete the procedure. The new subtyping system provides a clear guideline for the preparation of preoperative treatment plannings and selection of equipment including medications and tools for thrombolysis, as well as the proper selection of percutaneous puncture routes and endovascular treatment methods (**Table 6**).

Hepatic vein obstruction subtypes	**Inferior vena cava obstructive subtypes**	**Mixed-type occlusions**
Hepatic vein/hepatic venous membranous obstruction (**Figure 15**)	Inferior vena cava membranous perforation (**Figure 19**)	Hepatic vein and inferior vena cava occlusion (**Figure 23**)
Hepatic venous segmental obstruction (**Figure 16**)	Inferior vena cava membranous obstruction (**Figure 20**)	Hepatic vein and inferior vena cava occlusion with thrombosis (**Figure 24**)
Extensive hepatic vein occlusion (**Figure 17**)	Inferior vena cava segmental obstruction (**Figure 21**)	
Hepatic vein occlusion combined with thrombosis (**Figure 18**)	Inferior vena cava obstruction with thrombosis (**Figure 22**)	

Table 5.
Ten subtypes of Budd-Chiari syndrome.

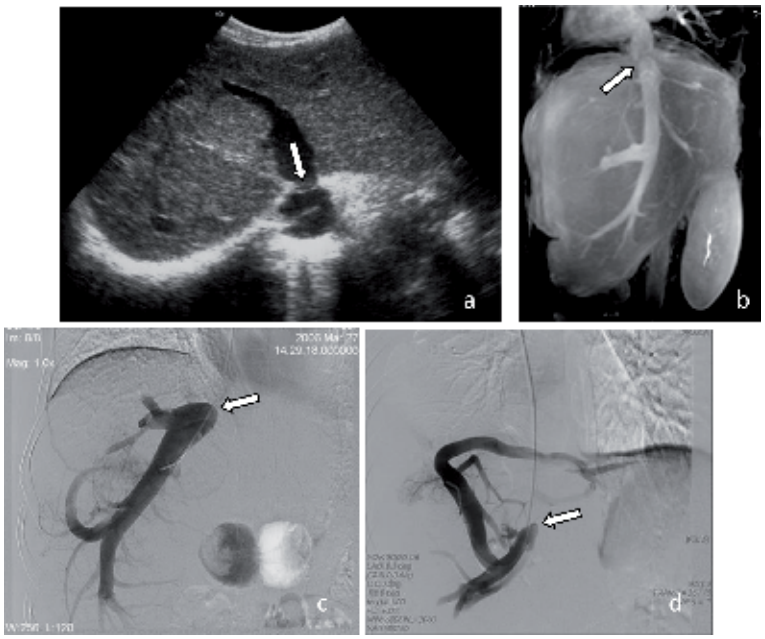

Figure 15.
Hepatic vein/hepatic venous membranous obstruction. (a) An ultrasound showing the septum at the left hepatic vein opening (arrow). (b) MRV showing the venous septum in the IVC (arrow). (c) DSA showing membranous venous occlusion in the right hepatic vein (arrow). (d) DSA showing membranous obstruction of the accessory hepatic vein (arrow).

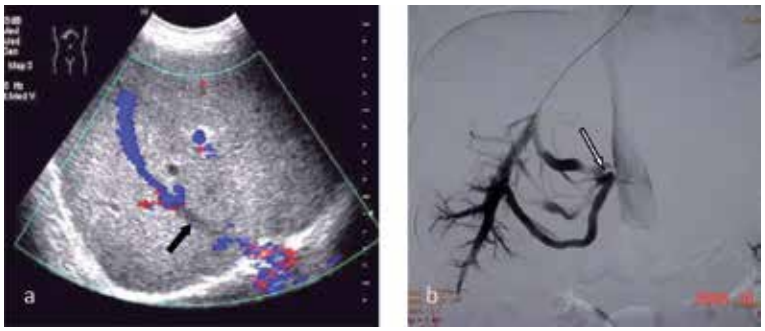

Figure 16.
Hepatic venous segmental obstruction. (a) An ultrasound showing the segmental obstruction (black arrow) of the right hepatic vein. (b) DSA showing segmental occlusion of the middle hepatic vein along with membranous obstruction (white arrow) of parahepatic venous structures.

6.7 New perspectives

6.7.1 Anatomical occlusion versus functional occlusion

According to our data analysis of more than 2400 cases, the incidence of obstruction of the left hepatic vein in patients with BCS is higher than 95%. Due to the small volume and smaller venous return of the left hepatic lobe, the outcome of occlusion of the left hepatic vein is minimal since collateral branches can form between the left hepatic vein, right hepatic vein, and left inferior diaphragmatic vein. Due to the presence of the collateral branches, even if the left hepatic vein and the middle hepatic vein are occluded, venous return can be entirely compensated by the venous return of the right hepatic vein or accessory hepatic vein. Therefore, we

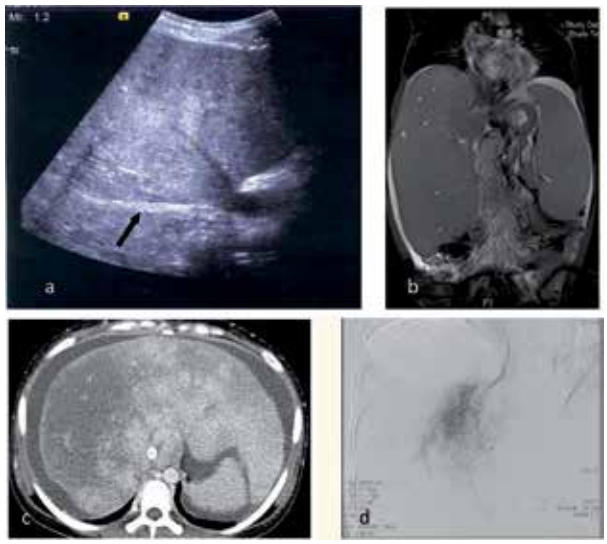

Figure 17.
Extensive hepatic vein occlusion. (a) An ultrasound showing the right hepatic venous occlusion of the liver with hyperechoic texture. The right hepatic vein is faintly depicted (black arrow), and the left hepatic vein is small in caliber. (b) MR showing hepatosplenomegaly. Hepatic veins are few and small in calibers. (c) Enhanced CT showing hepatomegaly and heterogeneous parenchymal enhancements. (d) DSA showing the disappearance of the main trunk of the hepatic vein and small reticular-shaped collateral vessels.

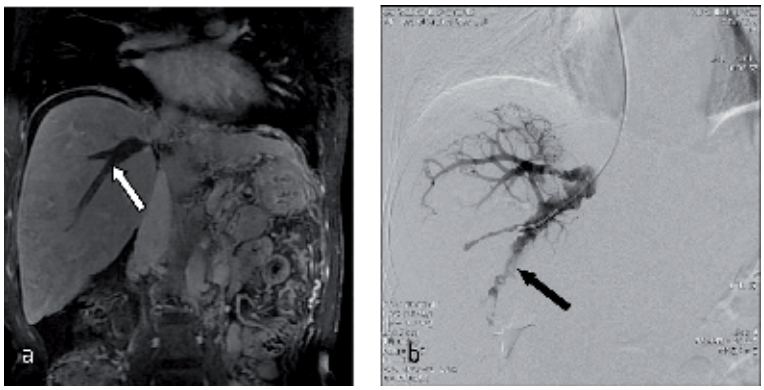

Figure 18.
Hepatic vein occlusion combined with thrombosis. (a) MRI showing the right hepatic vein occlusion with thrombosis (white arrow). (b) DSA showing hepatic venous occlusion with thrombosis (black arrow).

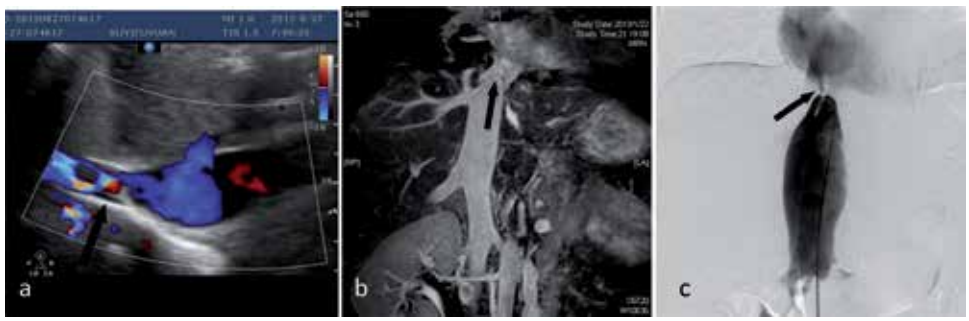

Figure 19.
Inferior vena cava membranous obstruction with a tiny perforation. (a) Color-flow mapping showing membranous obstruction (black arrow) of the inferior vena cava. (b) MRI showing membranous obstruction (black arrow) of the inferior vena cava. (c) DSA showing membranous obstruction of the inferior vena cava with a tiny perforation (black arrow).

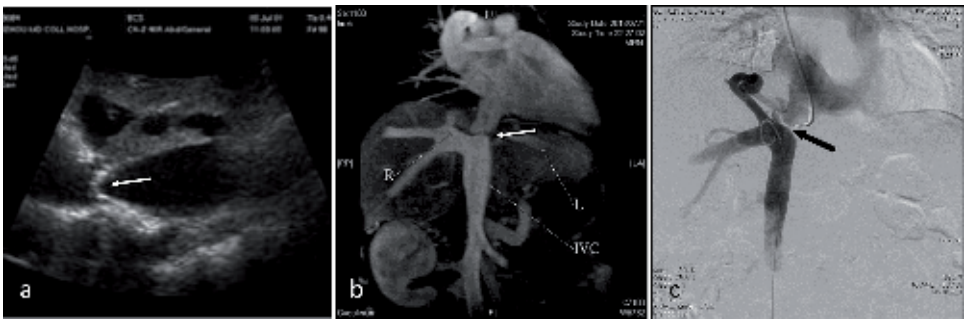

Figure 20.
Inferior vena cava membranous obstruction. (a) An ultrasound showing the vena cava septum as an echoic texture (white arrow). (b) MRV showing hypointense inferior vena cava septum (white arrow) right above the hepatic vein opening. (c) DSA showing membranous occlusion (black arrow) of the inferior vena cava.

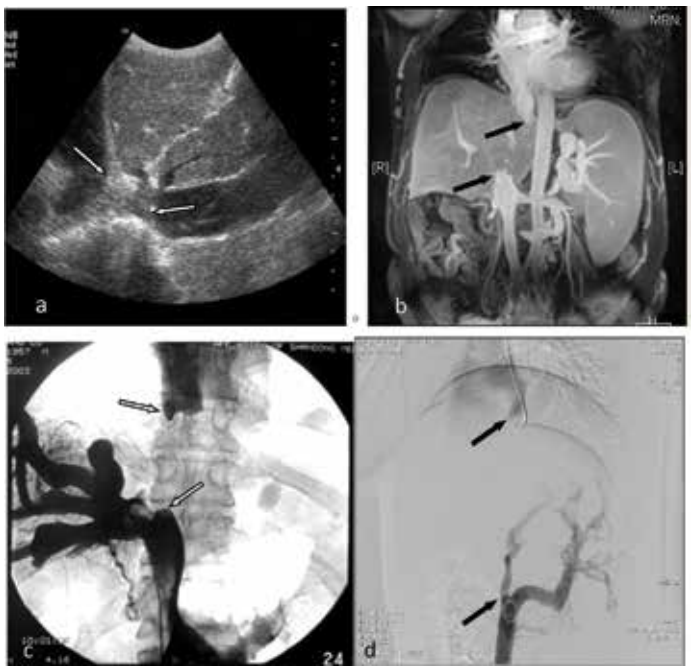

Figure 21.
Inferior vena cava segmental obstruction. (a) An ultrasound showing segmental occlusion (white arrows) of the inferior vena cava. (b) MRV showing a long segmental occlusion (black arrows) of the inferior vena cava. (c) DSA showing a long segmental occlusion (black arrows) of the inferior vena cava. (d) DSA projected in a lateral view showing an ultra-long segmental occlusion (black arrows) of the inferior vena cava.

still subtype cases with obstruction of the left hepatic vein and middle hepatic vein as isolated inferior vena cava obstruction type.

6.7.2 Accessory hepatic veins

In addition to the three hepatic veins, there are scattered small hepatic veins, collectively called the accessory hepatic vein (AHV) or the short hepatic veins, that drain directly into the IVC. After conducting anatomic researches, Liu et al. find that there are two primary sources of AHV: one is from the caudate lobar vein and the other from the right posterior hepatic vein. However, since most of the AHV are too small and are not the central draining vein of the liver, they are often neglected [65]. However, in patients with BCS, when hepatic vein occlusion occurs, AHV is

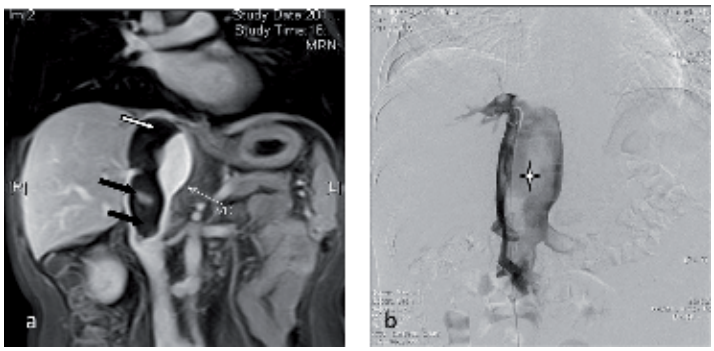

Figure 22.
Inferior vena cava obstruction with massive thrombosis. (a) Gadolinium-enhanced MRI demonstrating massive thrombi of various ages (black arrows and white arrow) in the IVC below the level of obstruction. (b) DSA showing membranous obstruction in the IVC along with bulky thrombi (asterisk).

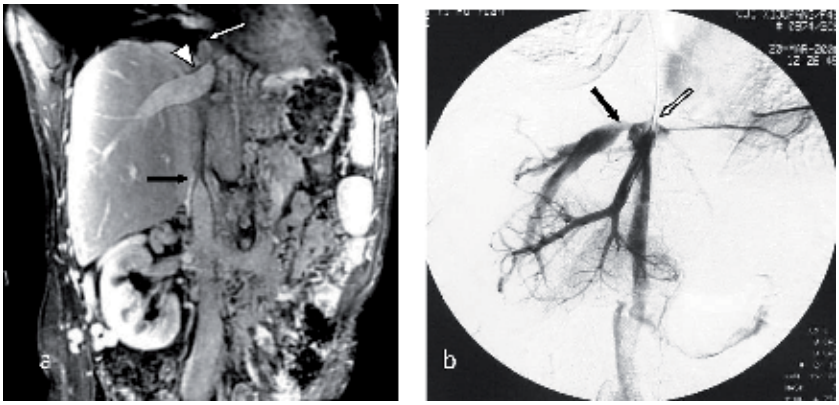

Figure 23.
Hepatic vein and inferior vena cava occlusion. (a) MRI showing right hepatic venous membranous obstruction (white arrowhead) with segmental occlusion (black and white arrows) of the inferior vena cava. (b) DSA showing membranous occlusions of the right hepatic vein (black arrow) and inferior vena cava (white arrow).

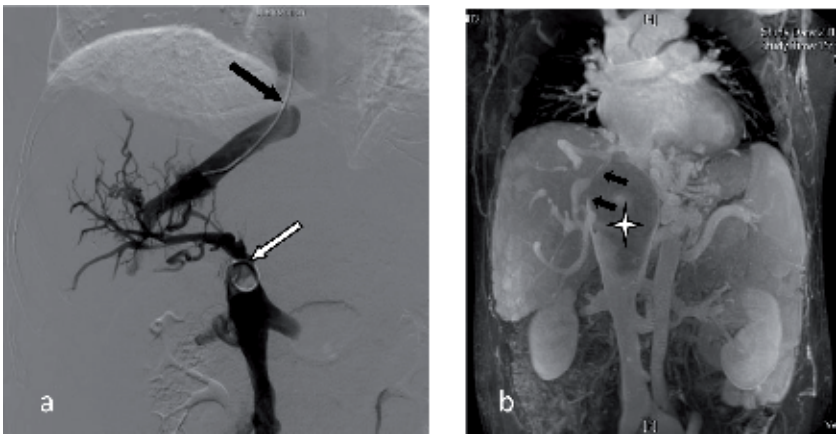

Figure 24.
Hepatic vein and inferior vena cava occlusions with thrombosis. (a) DSA showing right hepatic vein occlusion (black arrow) and IVC segmental occlusion with massive thrombosis (white arrow). (b) MRI showing occlusions of the hepatic vein (black arrows) and IVC with massive thrombi of various ages (asterisk).

Subtype	Endovascular therapy
Hepatic vein with membranous obstruction	Balloon dilatation
Hepatic vein segmental obstruction	Balloon dilatation + stent
Hepatic vein extensive obstruction	TIPS, hepatic vein reconstruction
Hepatic vein occlusion with thrombosis	Thrombolysis and balloon dilatation
Inferior vena cava membranous axonal	Balloon dilatation
Inferior vena cava membranous obstruction	Balloon dilatation
Inferior vena cava segmental obstruction	Balloon dilatation + stent
Inferior vena cava obstruction with thrombosis	Thrombolysis + balloon dilation/stent
Inferior vena cava and hepatic vein obstruction	Balloon dilation/stent
Inferior vena cava and hepatic vein obstruction with thrombosis	Thrombolysis + balloon dilation/stent

Table 6.
Selection of endovascular treatment methods based on the subtypes of BCS.

the main channel for venous return. Gai performed an ultrasound investigation on 244 BCS patients and found 191 (78.3%) cases presented with AHV. Among the 244 BCS patients, 209 had hepatic caudate lobar veins with an average diameter of (7.88 ± 2.78) mm, and 147 had a right inferior hepatic vein with an average diameter of (9.50 ± 3.11) mm [66]. During expansion of the AHV lumen, collateral branches between the hepatic vein and the accessory hepatic vein can fully compensate the hepatic venous return (see **Figure 21c**). In cases accompanied with IVC obstruction, the degree of IVC obstruction aggravates the expansion of AHV lumen. The accessory hepatic vein can also get obstructed. When the diameter of the AHV reaches 6 mm, it has sufficient compensatory capacity. Therefore, the interventional treatment of the obstructed accessory hepatic vein above 6 mm is equivalent to the treatment of the hepatic vein. In short, the accessory hepatic vein is of equal value to the hepatic vein in the diagnosis and treatment of BCS [67].

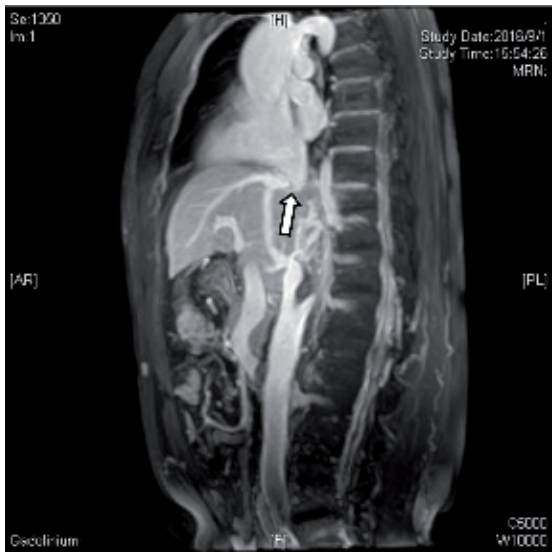

Figure 25.
MRV showing that the middle hepatic venous opening (hatched arrow) is above the inferior vena cava obstruction.

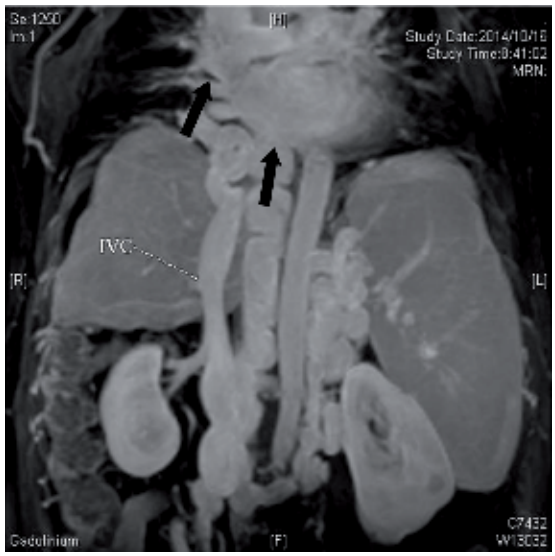

Figure 26.
MRV showing inferior vena cava obstruction with substantial azygos vein (black arrows) compensation.

6.7.3 Inferior vena cava septum and position of hepatic vein opening

The location of the inferior vena cava septum is generally above the hepatic vein opening, often causing hepatic venous blood flow obstruction. As the number of BCS cases increases, we find cases with the left hepatic vein and middle hepatic vein locating above the inferior vena cava septum. Dr. Zhang of the Chinese Department of Vascular Surgery also found a case (**Figure 25**) with the hepatic vein opening directly above the inferior vena cava septum while providing surgical resection of inferior vena cava septum. Although the numbers of this kind of cases are exceptionally few, the consideration on redefining BCS may be raised.

6.7.4 Azygos veins and its collateral branches

When hepatic vein becomes obstructed, the establishment of collateral branches between the intrahepatic veins is simple, but it is difficult for collateral branches to develop outside of the liver. This can result in portal hypertension with poor prognosis. In contrast, the establishment of the collateral branches after the inferior vena cava obstruction is relatively easy and extensive (see **Figure 26**). The azygous vein is the most crucial collateral branch when inferior vena cava obstruction occurs. The azygous vein can expand to a diameter of 2 cm (**Figure 21**) and compensate for the venous return of the inferior vena cava, and the patient usually can survive longer. Therefore, the severity of clinical symptoms of BCS is closely related to the compensatory capacity of the collateral circulation.

6.7.5 Closed collateral branch

After significant obstruction of the inferior vena cava, the superficial and deep vein begins to form collateral and communicating branches. In some cases, one or more collateral branches can appear above the site of inferior vena cava obstruction, with the diameter of reaching 2–3 mm. It can appear as single or multiple saclike structures, which are difficult to detect on preoperative ultrasound, CT, and MRV. However, DSA can easily show the obstruction and collateral branches

which play a vital blood flow compensation. During endovascular treatment, the existence of this collateral branch poses a potential risk. Since the collateral branches cannot be wholly identified under fluoroscopy, they may be ruptured during balloon dilatation, resulting in fatal intra-abdominal or intrathoracic bleeding. Thus, it is essential to be aware of this situation to ensure the safety of endovascular therapy.

7. Conclusion

With the adjunct use of PMAT incorporated in percutaneous CDT technology dedicated to the sophisticated endovascular management of DVT and DVT-related syndrome, the prevalence of PTS of moderate to severe degree and the intractable pain associated with advanced venous hypertension can be improved substantially. However, a randomized controlled study, comparing the adjunct use of PMAT or not, is demanded to offer convincing evidence. In conjunction with PTA and stenting after successful PMAT, symptomatic MTS can be well managed in terms of high technical success rate and midterm patency rate with acceptable minor complications. Along with the appreciations of newly identified pathophysiology and the creation of a new classification of subtypes, the selection of optimal mode of endovascular interventions in BCS may be solidly anticipated.

Literature search methods

The key references used in this manuscript are primary obtained using PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and the textbooks "Abrams' Angiography: Interventional Radiology Third Edition" and "Venous Interventional Radiology With Clinical Perspectives 2nd Edition," as listed in References section. Some co-authors' references and new concepts are acquired from the recent Chinese radiology professional committee discussions.

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References

[1] U.S. Department of Health and Human Service. The Surgeon General's Call to Action to Prevent Deep Thrombosis and Pulmonary Embolism. Washington, DC: Author; 2008

[2] Salzman EW, Hirsh J. The epidemiology, pathogenesis and natural history of venoas thrombosis. In: Columan RW, Hirsh J, Marder VJ, Salzman EW, editors. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. Philadelphia, PA: JB Lippincott; 1994. pp. 1275-1296

[3] Dähnert W. Deep vein thrombosis. In: Radiology Review Manual. 3rd ed. Baltimore: Williams & Wilkins; 1996. pp. 464-463

[4] White RH, Related Articles, et al. The epidemiology of venous thromboembolism. Circulation. 2003;**107**(23 supply 1):14-18

[5] Foley WD, Middleton WD, Lawson TL, Erickson S, Quiroz FA, Macrander S. Color Doppler ultrasound imaging of lower-extremity venous disease. American Journal of Roentgenology. 1989;**152**:371-376

[6] Rose SC, Zwiebel WJ, Nelson BD, Priest DL, Knighton RA, Brown JW, et al. Symptomatic lower extremity deep venous thrombosis: Accuracy, limitations, and role of color duplex flow imaging in diagnosis. Radiology. 1990;**175**:639-644

[7] Rose SC, Zwiebel WJ, Murdock LE, Hofmann AA, Priest DL, Knighton RA, et al. Insensitivity of color Doppler flow imaging for detection of acute calf deep venous thrombosis in asymptomatic postoperative patients. Radiology. 1993;**4**:111-117

[8] Haines ST, Bussey HI. Diagnosis of deep vein thrombosis. American Journal of Health-System Pharmacy. 1997;**54**:66-74

[9] Wille-Jørgensen P, Borris L, Jørgensen LN, Hauch O, Lassen MR, Nehen AM, et al. Phlebography as the gold standard in thromboprophylactic studies? A multicenter interobserver variation study. Acta Radiologica. 1992;**33**(1):24-28

[10] Savader SJ, Trerotola SO. Venous Interventional Radiology with Clinical Perspective. 2nd ed. Thieme; 2000. pp. 445-454

[11] Moody AR, Pollock JG, O'Connor AR, Bagnall M. Lower-limb deep venous thrombosis: Direct MR imaging of the thrombus. Radiology. 1998;**209**(2):349-355

[12] Fraser DG, Moody AR, Morgan PS, Martel AL, Davidson I. Diagnosis of lower-limb deep venous thrombosis: A prospective blinded study of magnetic resonance direct thrombus imaging. Annals of Internal Medicine. 2002;**136**(2):89-98

[13] Westerbeek RE, Van Rooden CJ, Tan M, Van Gils AP, Kok S, De Bats MJ, et al. Magnetic resonance direct thrombus imaging of the evolution of acute deep vein thrombosis of the leg. Journal of Thrombosis and Haemostasis. 2008;**6**(7):1087-1092

[14] Garg K, Kemp JL, Wojcik D, Hoehn S, Johnston RJ, Macey LC, et al. Thromboembolic disease: Comparison of combined CT pulmonary angiography and venography with bilateral leg sonography in 70 patients. American Journal of Roentgenology. 2000;**175**(4):997-1001

[15] Garg K, Mao J. Deep venous thrombosis: Spectrum of findings and pitfalls in interpretation on CT venography. American Journal of Roentgenology. 2001;**177**(2):319-323

[16] Thomas SM, Goodacre SW, Sampson FC, van Beek EJ. Diagnostic

value of CT for deep vein thrombosis: Results of a systematic review and meta-analysis. Clinical Radiology. 2008;**63**(3):299-304

[17] Goldhaber SZ, Buring JE, Lipnick RJ, Hennekens CH. Pooled analyses of randomized trials of streptokinase and heparin in phlebographically documented acute deep venous thrombosis. The American Journal of Medicine. 1984;**76**(3):393-397

[18] Bjarnason H, Kruse JR, Asinger DA, Nazarian GK, Dietz CA Jr, Caldwell MD, et al. Iliofemoral deep venous thrombosis: Safety and efficacy outcome during 5 years of catheter-directed thrombolytic therapy. Journal of Vascular and Interventional Radiology. 1997;**8**(3):405-418

[19] Mewissen MW, Seabrook GR, Meissner MH, Cynamon J, Labropoulos N, Haughton SH. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: Report of a national multicenter registry. Radiology. 1999;**211**(1):39-49

[20] Gloviczki P. Handbook of Venous Disorder Guidelines of the American Venous Forum. 3rd ed. London, England: Edward Arnold Publishers; 2009

[21] Enden T, Haig Y, Kløw NE, Slagsvold CE, Sandvik L, Ghanima W, et al. CaVenT study group. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): A randomised controlled trial. Lancet. 2012;**379**:31-38

[22] Vedantham S, Goldhaber SZ, Julian JA, Kahn SR, Jaff MR, et al. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. The New England Journal of Medicine. 2017;**377**:2240-2252

[23] Comerota AJ, Throm RC, Mathias SD, Haughton S, Mewissen M. Catheter-directed thrombolysis for iliofemoral deep venous thrombosis improves health-related quality of life. Journal of Vascular Surgery. 2000;**32**:130-137

[24] Elsharawy M, Elzayat E. Early results of thrombolysis vs anticoagulation in iliofemoral venous thrombosis. A randomised clinical trial. European Journal of Vascular Surgery. 2002;**24**:209-214

[25] AbuRahma AF, Perkins SE, Wulu JT, Ng HK. Iliofemoral deep vein thrombosis: Conventional therapy versus lysis and percutaneous transluminal angioplasty and stenting. Annals of Surgery. 2001;**233**:752-760

[26] Semba CP, Dake MD. Iliofemoral deep venous thrombosis: Aggressive therapy with catheter-directed thrombolysis. Radiology. 1994;**191**(2):487-494

[27] Vedantham S, Grassi CJ, Ferral H, et al. Reporting standards for endovascular treatment of lower extremity deep vein thrombosis. Journal of Vascular and Interventional Radiology. 2006;**17**(3):417-434

[28] Ferris EJ, Lim WN, Smith PL, Casali R. May-Thurner syndrome. Radiology. 1983;**147**(1):29-31

[29] Mc Murrich JP. The valves of the iliac vein. British Medical Journal. 1906;**2**:1699-1700

[30] May R, Thurner J. The cause of the predominantly sinistral occurrence of thrombosis of the pelvic veins. Angiology. 1957;**8**(5):419-427

[31] Negus D, Fletcher EW, Cockett FB, Thomas ML. Compression and band formation at the mouth of the left common iliac vein. The British Journal of Surgery. 1968;**55**(5):369-374

[32] Vollman JF, Hutschenreiter S. Vascular endoscopy for venous thrombectomy. In: Moore WB, Alin SS, editors. Endovascular Surgery.

Philadelphia: WB Saunders; 1989. pp. 65-73

[33] Juhan CM, Alimi YS, Barthelemy PJ, Fabre DF, Riviere CS. Late results of iliofemoral venous thrombectomy. Journal of Vascular Surgery. 1997;**25**(3): 417-422

[34] Nagayo M, Nakayama O. Ueber die Stenose bzw. Obliteration der linken V. iliaca an der Einmundungsstelle in die Hohlvene. Deutsche Medizinische Wochenschrift. 1912;**38**:749-751

[35] Akaneema J et al. Stricture of opening in the left common iliac vein in Korean people. Proceedings of The Japanese Society of Pathology. 1932;**2**:595-598

[36] Mitsuoka H, Ohta T, Hayashi S, Yokoi T, Arima T, Asamoto K, et al. Histological study on the left common iliac vein spur. Annals of Vascular Diseases. 2014;**7**(3):261-265

[37] Forauer AR, Gemmete JJ, Dasika NL, Cho KJ, Williams DM. Intravascular ultrasound in the diagnosis and treatment of iliac vein compression (May-Thurner) syndrome. Journal of Vascular and Interventional Radiology. 2002;**13**(5):523-527

[38] Brinegar KN, Sheth RA, Khademhosseini A, Bautista J, Oklu R. Iliac vein compression syndrome: Clinical, imaging and pathologic findings. World Journal of Radiology. 2015;**7**(11):375-381

[39] Cockett FB, Thomas ML, Negus D. Iliac vein compression. Its relation to iliofemoral thrombosis and the post-thrombotic syndrome. British Medical Journal. 1967;**2**(5543):14-19

[40] Hurst DR, Forauer AR, Bloom JR, Greenfield LJ, Wakefield TW, Williams DM. Diagnosis and endovascular treatment of iliocaval compression syndrome. Journal of Vascular Surgery. 2001;**34**(1):106-113

[41] Shebel ND, Whalen CC. Diagnosis and management of iliac vein compression syndrome. Journal of Vascular Nursing. 2005;**23**(1):10-17; quiz 18-9

[42] Brazeau NF, Harvey HB, Pinto EG, Deipolyi A, Hesketh RL, Oklu R. May-Thurner syndrome: Diagnosis and management. VASA. 2013;**42**(2):96-105

[43] Ibrahim W, Al Safran Z, Hasan H, Zeid WA. Endovascular management of May-Thurner syndrome. Annals of Vascular Diseases. 2012;**5**(2):217-221

[44] Kim JY, Choi D, Ko YG, Park S, Jang Y, Lee DY. Treatment of May-Thurner syndrome with catheter-guided local thrombolysis and stent insertion. Korean Circulation Journal. 2004;**34**:655-659

[45] Chung JW, Yoon CJ, Jung SI, Kim HC, Lee W, Kim YI, et al. Acute iliofemoral deep vein thrombosis: Evaluation of underlying anatomic abnormalities by spiral CT venography. Journal of Vascular and Interventional Radiology. 2004;**15**(3):249-256

[46] Oguzkurt L, Tercan F, Pourbagher MA, Kizilkilic O, Turkoz R, Boyvat F. Computed tomography findings in 10 cases of iliac vein compression (May-Thurner) syndrome. European Journal of Radiology. 2005;**55**(3):421-425

[47] Liu Z, Gao N, Shen L, Yang J, Zhu Y, Li Z, et al. Endovascular treatment for symptomatic iliac vein compression syndrome: A prospective consecutive series of 48 patients. Annals of Vascular Surgery. 2014;**28**(3):695-704

[48] Hölper P, Kotelis D, Attigah N, Hyhlik-Dürr A, Böckler D. Longterm results after surgical thrombectomy and simultaneous stenting for symptomatic iliofemoral venous thrombosis. European Journal of Vascular and Endovascular Surgery. 2010;**39**:349-355

[49] Zhang W, Qi X, Zhang X, et al. Budd-Chiari syndrome in China: A systematic analysis of epidemiological features based on the Chinese literature survey. Gastroenterology Research and Practice. 2015;**2015**:738548

[50] Martens P, Nevens F. Budd-Chiari syndrome. United European Gastroenterology Journal. 2015;**3**(6):489-500

[51] Han X, Zu M. Study the significance of VEGF abnormal expression in membranous obstruction with Budd-Chiari syndrome. Contemporary Medicine. 2010;**16**(35):672-674

[52] Guo C, Bian J, Wang Y. Effects of multiple elements in drinking water on inferior vena cava membranous obstruction type of the Budd-Chiari syndrome in Heze area of Shandong province. Chinese Journal of Endemiology. 2005;**2**:207-209

[53] Zhuang Y, Zu M, Li J, et al. Serum iodine is increased in subjects having Budd-Chiari syndrome. Biological Trace Element Research. 2015;**168**:21-24

[54] Zu M, Xu H, Gu Y, et al. Treatments to deal with difficult cases and complications during interventional therapy for Budd-Chiari syndrome: Report of 1859 cases. Chinese Journal of Bases and Clinics in General Surgery. 2014;**12**:1487-1494

[55] Wang L, Zu M, Teng F, et al. Budd-Chiari syndrome in youth: Clinical features and interventional therapy. Chinese Journal of General Surgery. 2013;**28**(9):686-689

[56] Teng F, Zu MH, Hua QJ. Correlations of iodide ions with vascular endothelial growth factor and its receptors during the proliferation of vascular endothelial cells. Genetics and Molecular Research. 2014;**13**(3):6439-6447. DOI: 10.4238/2014.August.25.7

[57] Hua Q J, Zu MH, Teng F, et al. Research on the relationship between bFGF, FGFR2 and the fibroblast proliferation promoted by high density iodine. Journal of Interventional Radiology. 2013;**22**(12):1016-1020

[58] Teng F, Zu MH, Hua Q, et al. The relationship between iodide ion and vascular endothelial growth factor together with its receptor in vascular endothelial cell proliferation. Journal of Interventional Radiology. 2013;**22**(6):486-489

[59] Kiladjian J, Cervantes F, Leebeek FW, et al. The impact of JAK2 and MPL mutations on diagnosis and prognosis of splanchnic vein thrombosis: A report on 241 cases. Blood. 2008;**111**:4922-4929

[60] Wang H, Sun G, Zhang PJ, et al. JAK2 V617F mutation and 46/1 haplotype in Chinese Budd-Chiari syndrome patients. Journal of Gastroenterology and Hepatology. 2014;**29**:208-214

[61] Xu K, Li L. Budd-Chiari syndrome: CT and MR findings. Journal of Interventional Radiology. 2008;**17**(4):294-298

[62] Expert Committee on Vena Cava Obstruction Specialized Committee of Endovasculogy, Chinese Medical Doctor Association, Maoheng Z. Expert consensus on the definition of "membranous obstruction" and "segmental obstruction" of the inferior vena cava and hepatic vein in Budd-Chiari syndrome. Journal of Interventional Radiology. 2016;**25**(7):559-561

[63] Specialized Committee of Intervention, Chinese Radiology Professional Committee, Maoheng Z. Expert consensus on interventional diagnosis and treatment of Budd-Chiari syndrome. Chinese Journal of Radiology. 2010;**44**(4):345-249

[64] Expert Committee on Vena Cava Obstruction Specialized Committee of Endovasculogy, Chinese Medical Doctor Association, Maoheng Z. Expert consensus on the classification of subtype in Budd-Chiari syndrome. Journal of Interventional Radiology. 2017;**26**(3):195-200

[65] Liu S, Xu W, Luan M. Applied anatomy of vascular architecture in caudate lobe of liver. Chinese Journal of Clinical Anatomy. 1991;**9**(3):138-142

[66] Gai Y. Ultrasonic diagnosis of accessory hepatic vein and its lesion in Budd-Chiari syndrome. Chinese Journal of Ultrasound Imaging. 2010;**26**(7):641-644

[67] Zu MH, Xu H, Gu Y, et al. The value of accessory hepatic vein in Budd-Chiari syndrome. Chinese Journal of Radiology. 1998;**32**(9):616-619

Chapter 9

Bullet and Shrapnel Embolism: When "Uncommon" Meets "Dangerous"

Stephen D. Dingley, Zachary E. Darby, Jennifer C.B. Irick, Gregory Domer and Stanislaw P. Stawicki

Abstract

Bullet and shrapnel embolism (BSE) is well described in the literature. Despite that, its rare occurrence creates a diagnostic challenge for providers tending to penetrating trauma victims. As with other forms of embolic phenomena, cases of BSE require a blend of superb clinical expertise and experience, as well as a high diagnostic index of suspicion. Management is highly individualized and spans a broad spectrum of options from "watchful waiting" to open heart surgery. Due to the risk of retained projectile migration through tissues, including erosion into surrounding anatomic structures, non-operative approaches warrant long-term clinical surveillance. When promptly recognized and treated appropriately, patients with BSE can be expected to have excellent clinical outcomes.

Keywords: bullet embolism, clinical management, diagnosis, shrapnel embolism, treatment

1. Introduction

With approximately only 300 published cases to date, bullet and shrapnel emboli (BSE) constitute a rare, but well-established, phenomenon in trauma [1–3]. The incidence of BSE has been reported to range between 0.3 and 1.1% of penetrating injuries, depending on the type of projectile, the setting of injury, and various patient characteristics [4].

The literature on the topic is heavily case-based, limiting both the generalizability and applicability of the findings [1–3, 5]. Consequently, clinical progress appears to follow the publication of major case series and definitive reviews on the topic. A 1950 review by Barrett presented a collected series of foreign bodies which have embolized into the cardiovascular system [2]. In the early 1960s, Kinmonth et al. published a case and a commentary titled, "Gunshot wounds of the heart with embolism" [5]. In that report, the authors describe open heart surgery using extracorporeal circulatory support to extract loose shotgun pellets from cardiac cavities [5]. In the late 1970s, Mattox et al. [6] published an important series describing clinical management of nearly 30 cases of intravascular migratory bullets. Over the past three decades, controversies persisted regarding the preferred stance on BSE, ranging from "watchful waiting" to "mandatory removal" [1, 7]. Today, approaches to BSE involve state-of-the-art diagnostic and therapeutic developments, from

high-resolution computed tomography (CT) imaging to endovascular retrieval techniques [8]. In this chapter, we provide an overview of BSE, starting with case-based historical perspective and ending with a summary of modern developments in this rarely encountered but important area of penetrating trauma management.

2. Case-based historical perspective

Surgical case history is rich with fascinating stories demonstrating both the natural history and the evolution of clinical management of BSE. In an 1834 report, Davis describes what may well be the first formal case report of BSE. The patient was a 10-year-old boy who, while making a gun, accidentally set off the gunpowder and was shot with a 3-inch piece of wood. This pierced his chest to the right of the sternum between the 3rd and 4th ribs. The patient lived for 37 days and Davis reported that the autopsy showed no injury to the heart. Instead, it appeared that the object had pierced through the lung and into vena cava, from where it traveled to the right ventricle (RV) [9].

Another early report originated during the First Anglo-Burmese War in 1824, whereby a soldier suffered a rifle shot into the left axilla [2]. He was subsequently noted to have drainage of blood, air, and later purulent material from his wound. Unfortunately, he went on to succumb to this injury 3 days later. An autopsy showed the tract of the round bullet into the left lung, with the projectile eventually migrating into the left ventricle (LV). Of note, there was no direct injury to the heart. The bullet appeared to have penetrated a pulmonary vein and traveled back to the heart [2].

Despite his skeptical stance toward the original report by Davis [9], Bland-Sutton in 1919 stated that "in regard to the embolic theory that (Davis) advanced to explain the presence of the stick in the ventricle" it was important to emphasize that "at the date of the accident surgeons knew nothing of the transport of blood-clot either to or from the heart" [10]. It was only around that time that Virchow's theory regarding deep venous thrombosis (DVT) and pulmonary embolism (PE) was coming into formation [11, 12].

Even during the time of Barrett's review in 1950 with comparatively limited access to information and drastically fewer publications than today, he stated that "any writer who believes his case to be singular or unique is probably not well-informed" [2]. The same point continues to be true despite tremendous progress in trauma surgery since the 1950s. Therefore, it is the authors' duty to inform the reader that although cases of BSE are rare, they have indeed been well-documented in the literature and tend to follow a number of fairly typical patterns [7, 13–16]. The modern surgeon or interventionalist must be aware not only of the presence of BSE but also key aspects of diagnosis, clinical management approaches, and possible short- and long-term outcomes [1, 7].

3. Anatomic, pathophysiological, and diagnostic considerations

A bullet or shrapnel may undergo embolization when it only penetrates a single vessel wall and subsequently enters the circulation [4, 8]. To cross only one vessel wall and come to rest within the vessel, the bullet or projectile must be of a smaller diameter than the vessel and must possess kinetic energy that allows the initial penetration but is insufficient to allow subsequent extravascular re-emergence. In general, a bullet or projectile without such narrowly defined characteristics will be highly unlikely to embolize. It is not surprising, therefore, that shotgun pellets and

22-caliber bullets are the two most common projectiles associated with BSE [3, 17, 18]. In fact, the vast majority of the cases in literature feature bullets that are 0.38 caliber and smaller, with only one recorded case of a 0.40 caliber bullet embolism [18]. An example of distal embolization of a shotgun pellet from the left brachiocephalic vein to the right ventricle is shown in **Figure 1** [19]. The incidence of shrapnel-related BSE may be even lower [4]. Projectiles from non-powdered guns, often regulated as recreational toys rather than weapons, can pose significant risk of embolization, with a recent systematic review calling attention to this public health risk in the pediatric population [20].

While it is often difficult to determine the presence of a BSE, there are several diagnostic findings that should raise suspicion. To start, an inconsistent number of entry and exit wounds may suggest a retained bullet. Secondly, when there is no evidence, either radiographically or clinically, of the bullet along the extrapolated course or if the bullet is found at a distant location, the possibility of BSE should be entertained. Lastly, when the piece of shrapnel (or a bullet) is seen in different locations on serial radiograph images, the phenomenon of a "migrating projectile" should increase the suspicion for BSE [21]. In one case, the application of whole body CT scan was instrumental in effectively localizing an embolized shrapnel fragment within the right mid-lobar pulmonary artery [4]. This particular example demonstrates that if small enough, grenade/bomb fragments can find their way to intravascular locations that are far removed from the area of original injury [4].

Projectiles can enter the cardiovascular system in a myriad of ways, including by direct entrance into an artery or vein, direct entrance into the chambers of the heart, or erosion from the lungs into the pulmonary vasculature [22]. According to a systematic review by Kuo et al. [20], reporting on 261 cases of BSE, embolization via venous route is most common (56%), with arterial (27%) and cardiac injuries (15%) seen less frequently. It is imperative that physicians are able to recognize the signs and symptoms of BSE so that timely and appropriate care can be instituted, with the goal of minimizing both associated complications and mortality. Because bullet embolism to the peripheral arterial system is an extremely rare phenomenon, early symptoms/manifestations are often misdiagnosed. Thus, in any patient presenting with history of exposure to bullet or shrapnel, as well as the appropriate clinical context and symptomatology, one must be vigilant in assessing for the

Figure 1.
*An example of a pellet from a shotgun blast to the left upper chest/proximal left arm area (*left*), with pellet embolization to the right ventricle (CT image,* right*).* Source*: Greaves [19]. Images reproduced and modified under the terms of the creative commons attribution license (http://creativecommons.org/licenses/by/2.0) which permits sharing and adapting of published work, as long as original work is properly cited/attributed.*

signs of acute arterial occlusion. These manifestations include the presence of pain, pallor, paresthesias, pulselessness, poikilothermia, and paralysis. The sequential appearance of these signs and symptoms is important when determining the duration of ischemia and prognosis through the Rutherford classification for acute limb ischemia. One must also consider the possibility of BSE when the wound–projectile locations are discordant on imaging. In most cases, an arterial projectile should be removed as soon as possible, even if the patient is initially asymptomatic as the embolus may become symptomatic, resulting in profound clinical sequelae and potential morbidity [23].

The reported distribution of BSE between venous, arterial, and cardiac portals of entry varies across published studies [4, 20, 21]. Nonetheless, clinical manifestations and management principles tend to be fairly consistent across the literature. The principal complication from arterial emboli is extremity or end-organ ischemia and thrombosis, which may occur due to the fact that intra-arterial projectiles travel with the flow of blood until they become wedged in smaller, more distal vessels. Given that significant proportion of BSE are sufficiently large to occlude a medium diameter vessel, the clinical relevance of bullet or shrapnel embolism becomes readily apparent. Not surprisingly, approximately 80% of arterial emboli are symptomatic and thus tend to present earlier and prompt more immediate treatment [3]. The foremost intervention utilized for arterial emboli is embolectomy, which is currently considered as the gold standard, with both open and endovascular techniques described [4, 24]. An example of a bullet causing left chest injury and subsequently embolizing to the left common femoral artery is provided in **Figure 2** [25]. The more commonly used military or civilian weapons fire bullets of 9 mm or greater diameter. This, in turn, means that such projectiles are unlikely to embolize beyond the iliac arteries distally or the common carotid and subclavian arteries proximally. At the same time, shotgun projectiles can be found virtually anywhere in peripheral arterial or venous circulation, with each pellet measuring approximately 2 mm in diameter [26, 27].

While venous BSE also typically follow the flow of blood, there are certain subtypes where venous emboli travel in a nonconforming fashion. For example, bullets may travel retrograde, due to the effects of gravity, within the venous system and thus manifest as "retrograde emboli"; however, this occurs only in an estimated 15% of instances [28]. Additionally, the projectile may cross over from venous to arterial circulation, becoming a "paradoxical" BSE. This usually requires the presence of a traumatic arteriovenous fistula (AVF) or an intracardiac defect, such as a patent foramen ovale or ventricular septal defect [3]. The incidence of such paradoxical emboli appears to be low, or approximately 2.4% [29]. In most (>80%) cases, therefore, venous BSE tend to migrate with the flow of blood and most commonly come to rest in the right heart or the pulmonary arterial (PA) system [1]. In a 2011 review, Schroeder et al. [30] pointed out that among 120 cases over a 90-year period, 83% of venous BSE terminate their intravascular journey in the PA or the right heart, while 4% remain in the peripheral venous system.

Embolized venous projectiles may be associated with a multitude of potential complications including, but not limited to, pulmonary artery embolism, cardiac valve dysfunction, dysrhythmias, intraventricular communications, cardiac conduction defects, endocarditis, abscess formation, sepsis, thrombosis, tissue erosion, hemorrhage, pseudoaneurysm, cardiac ischemia from erosion into coronary vessels, and thrombophlebitis [7, 21, 31]. However, it is important to keep in mind that venous emboli are only symptomatic in approximately one-third of cases, with clinically detectable complications related to the initial injury often noted months or even years later. Therefore, the preferred treatment approach, as well as the overall interventional aggressiveness, toward venous emboli has remained controversial [21, 32].

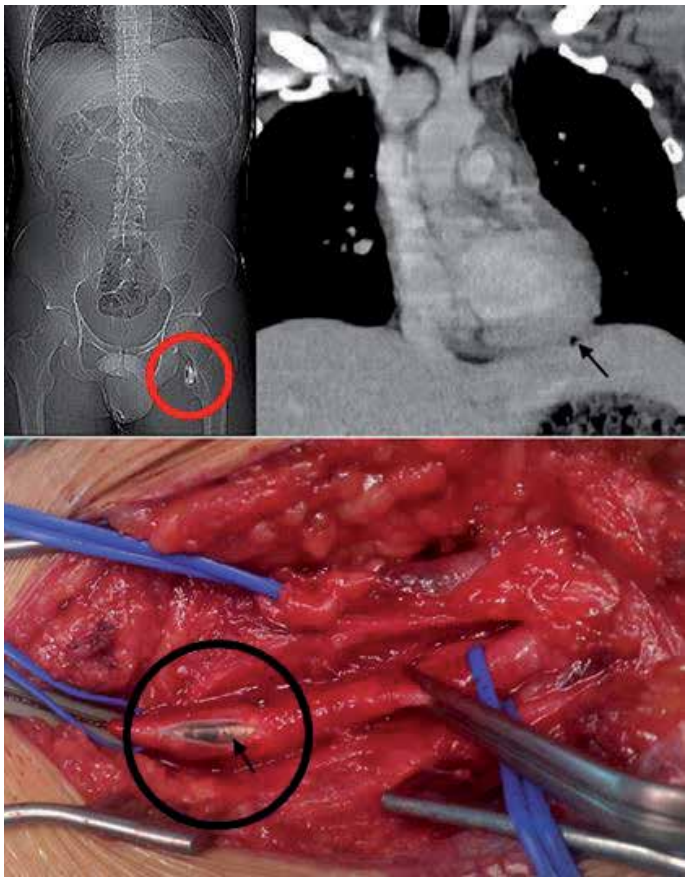

Figure 2.
An example showing images of a thoracic stray bullet that lodged within the left femoral artery. Intraoperative picture (bottom) shows the bullet immediately prior to its removal. Source*: Aoun et al. [25]. Images reproduced under the terms of the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/) which permits sharing of published work, as long as original work is properly credited.*

While a conservative approach in asymptomatic patients with retained projectiles may be warranted, there are case reports of patients presenting up to 6 years post-injury with sequelae of BSE [33]. Given the possibility for delayed morbidity, it is vital that medical specialties maintain a high index of suspicion for the risk of BSE in patients with even a remote history of penetrating trauma complicated by retained foreign objects, as these patients may present with relatively innocuous symptoms that are not obviously related to the initial insult.

4. Evolution of modern management approaches

As early as 1939, Decker published an important review of a large collected series of cases, seeking to determine the optimal management of intracardiac BSE [34]. Across the sources reviewed, 47 patients underwent BSE removal with a mortality rate of 17%, while 53 underwent observation with a mortality rate of 30%. These preliminary findings suggested a benefit to BSE removal [34]. In 1946, Harken and Zoll laid out the principles for removing BSE, which were subsequently used as the authoritative guidance for the next few decades [35]. To summarize, Harken and Zoll's guiding principles and goals of therapy included:

- The prevention of embolus of the foreign body or associated thrombus
- The reduction of the risk of bacterial endocarditis
- The prevention of recurrent pericardial effusion(s)
- The reduction of BSE-related myocardial damage, including any associated pain or other morbidity [35]

With advancements in surgical techniques, up to and including cardiopulmonary bypass, open BSE removal options became increasingly sophisticated and safer [36, 37]. The next advancement in management was made possible by further innovations in surgical technology that facilitated endovascular approaches, such as the removal of cardiac bullet "via a wire basket" [6].

In the late 1970s, Mattox et al. reported their experience involving 28 patients with intravascular bullet emboli [6]. In terms of projectile origin–destination pairings, this important article described BSE events as follows:

- Seven patients with peripheral vein to PA embolization
- Six patients with abdominal aorta to peripheral artery migration
- Five cases involving peripheral vein to heart embolization
- Four patients with thoracic aorta to peripheral artery migration
- Three cases of heart to peripheral artery embolization
- Two instances of heart to inferior vena cava (IVC) migration
- And finally one case of paradoxical embolism from IVC to abdominal aorta via penetration of the atrial septa [6]

In terms of management approaches, a total of 20 (71.4%) of projectiles were removed (12 peripheral artery, 5 heart, 2 PA, and 1 aortic bifurcation), removal of 1 projectile (3.6%) involving the carotid was unsuccessful, and 7 projectiles were left in place (5 in PA, 1 in hepatic vein, and 1 in renal vein) [6]. Morbidity in their series was limited to the bullet being left in place rather than efforts at retrieval. Two patients died, one from the propagation of carotid thrombosis and subsequent distal ischemia and the other from unrecognized cardiac trauma related to the bullet. Synthesizing their experience and prior literature reports, the authors recommended that most BSE should be removed [6].

Subsequent reports describe a wide range of therapeutic approaches, from clinical observation to intravascular BSE removal [7, 38–41]. With the entire spectrum of considerations within this evolving area being beyond the scope of the current chapter, the reader is encouraged to consult literature sources referenced below. More specifically, Kortbeek et al. provide an overview of conservative management approaches to pulmonary artery BSE [39]. Although potentially biased, their collected series suggests a favorable morbidity and mortality profile [39]. On the other hand, Shannon et al. [40] and Adegboyega et al. [7] advocate for mandatory BSE extraction, citing substantial morbidity and mortality of projectiles left in place [7, 40]. Furthermore, Norton et al. highlight the relative safety of modern cardiac procedures as part of their rationale for recommending the surgical approach [42].

The potential for delayed presentation has also been suggested as a rationale for surgical intervention [41]. More recently, percutaneous radiographic interventions have been increasingly common, as demonstrated by case reports of endovascular extraction of an intracardiac BSE [38, 43]. Yang et al. present a 12-case experience with nonsurgical management of intravascular foreign bodies [44].

In a recent review of 261 cases of BSE by Kuo et al. [20], authors propose a management strategy algorithm for intravascular projectiles, based on the evidence that foreign objects within the "left-sided" (e.g., left cardiac chambers, systemic arteries, pulmonary veins) circulation pose a greater risk of complications than those within the "right-sided" (e.g., right cardiac chambers, systemic veins, pulmonary arteries) circulation. Their algorithm considers the circulatory site (left vs. right), the presence or absence of symptoms, as well as presence of a cross-circulation shunt. They propose that all missiles to the "left-sided" circulation be removed either by operative or endovascular routes, while objects within the "right-sided" circulation may be safely managed conservatively if the patient is asymptomatic and does not have a right-to-left shunt [20].

Symptomatic BSEs can be defined as those leading to any of the potential complications mentioned throughout this article. Whenever possible, symptomatic BSE should be removed using endovascular approaches as the primary management option. Specific indications for removal include objects >5 mm in diameter, irregularly shaped objects, and projectiles that are freely mobile or only partially embedded within the myocardium [45, 46]. Advanced endovascular techniques can help facilitate safe removal of BSE, as exemplified by a 1980s report describing the first use of endovascular snare to retrieve a bullet embolus from the RV [47]. Since then multiple additional reports described various endovascular techniques and approaches for removing BSE across a broad range of anatomic locations [30, 44, 48, 49].

The management of asymptomatic venous emboli is not clearly defined and continues to be somewhat controversial. Nagy et al. [45] proposed criteria for non-operative management of such BSEs, recommending observation for right-sided cardiac and pulmonary artery BSE if there was no arrhythmia and no valvular dysfunction, the BSE was smooth and <5 mm, it was firmly in place, and there was no gastrointestinal contamination. In asymptomatic cases, the risk of surgical intervention involving the PA or RV must be weighed against the risk of delayed embolic or infective complications. When comparing available evidence, surgical intervention versus observation for venous BSE appears to produce no difference in outcome [39, 40]. Some authors have advocated for observation if an endovascular approach cannot be utilized given the arguably higher morbidity and mortality of open retrieval options, such as sternotomy and cardiopulmonary bypass [21]. The clinical heterogeneity of venous BSEs and limited clinical evidence have made it impractical to have a strict definition and a rigid approach toward conducting non-operative management. Instead, a set of loose recommendations evolved for outpatient follow-up featuring serial imaging, consideration of therapeutic anticoagulation, and potentially antibiotic prophylaxis when appropriate [24, 50].

5. Summary of specific clinical presentations

Due to the heterogeneity of anatomic locations and differing projectile-specific propensity to migrate and cause complications, a broad range of clinical presentations have been described. For example, cardiac-related findings may include valvular insufficiency [21, 31], broadly defined "cardiac irritability" such as the appearance of arrhythmias [41], and even sudden death [51]. Common pulmonary manifestations of BSE include chest pain, cough, dyspnea, and hemoptysis [22, 52]. Reported central

nervous system manifestations include both direct and paradoxical embolization leading to a stroke or other thromboembolic sequelae [21]. Peripheral vascular BSE may present with thrombophlebitis, venous thrombosis, vascular insufficiency, as well as limb ischemia [7, 21]. Finally, as outlined earlier in this chapter, one must keep in mind that arterial emboli will tend to present much earlier than venous emboli and that any major end-organ is potentially at risk of being affected [21].

6. Conclusions

Given the heterogeneity of presentations, projectile or shrapnel types, and variability of anatomic locations, management of BSE depends heavily on the clinical judgment of the treating physician. Specific considerations should take into account the anatomic location of the BSE, any associated symptoms, patient comorbidity profile, hospital endovascular capabilities, and the risk–benefit determination regarding more invasive interventions. Perhaps more important than the nuance in management is the necessity of recognition that BPE exists and is well-documented. Prompt workup to diagnose this phenomenon can be lifesaving and should guide the subsequent treatment. As our general understanding of the problem increases, the management of BSE will likely continue to move toward endovascular approaches, especially given the ongoing technological and procedural advances.

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References

[1] Wojda TR et al. Foreign intravascular object embolization and migration: Bullets, catheters, wires, stents, filters, and more. In: Embolic Diseases-Unusual Therapies and Challenges. London, UK: IntechOpen; 2017

[2] Barrett NR. Foreign bodies in the cardiovascular system. The British Journal of Surgery. 1950;**37**:416

[3] Lu K et al. Approach to management of intravascular missile emboli: Review of the literature and case report. The Western Journal of Emergency Medicine. 2015;**16**(4):489-496

[4] Khomenko I et al. Pulmonary artery embolism by a metal fragment after a booby trap explosion in a combat patient injured in the armed conflict in East Ukraine: A case report and review of the literature. Journal of Medical Case Reports. 2018;**12**(1):330

[5] Kinmonth J et al. Gunshot wounds of the heart with embolism. British Medical Journal. 1961;**2**(5268):1666

[6] Mattox KL et al. Intravascular migratory bullets. American Journal of Surgery. 1979;**137**(2):192-195

[7] Adegboyega PA, Sustento-Reodica N, Adesokan A. Arterial bullet embolism resulting in delayed vascular insufficiency: A rationale for mandatory extraction. Journal of Trauma and Acute Care Surgery. 1996;**41**(3):539-541

[8] Carter CO et al. Venous bullet embolism and subsequent endovascular retrieval—A case report and review of the literature. International Journal of Surgery Case Reports. 2012;**3**(12):581-583

[9] Davis T. Singular case of a foreign body found in the heart of a boy. Transactions of the Provincial Medical and Surgical Association. 1834;**2**:357-360

[10] Bland-Sutton J. Introductory. British Journal of Surgery. 1919;**7**(25):1-6

[11] Bagot CN, Arya R. Virchow and his triad: A question of attribution. British Journal of Haematology. 2008;**143**(2):180-190

[12] Szczepański M. Elements of Virchow's triad in the prevention and treatment of venous thrombosis. Polish Journal of Surgery. 2009;**81**(8):364-371

[13] Patel K et al. Bullet embolism. The Journal of Cardiovascular Surgery. 1989;**30**(4):584-590

[14] Trimble C. Arterial bullet embolism following thoracic gunshot wounds. Annals of Surgery. 1968;**168**(5):911

[15] Schurr M, McCord S, Croce M. Paradoxical bullet embolism: Case report and literature review. Journal of Trauma and Acute Care Surgery. 1996;**40**(6):1034-1036

[16] Bertoldo U et al. Retrograde venous bullet embolism: A rare occurrence—Case report and literature review. Journal of Trauma and Acute Care Surgery. 2004;**57**(1):187-192

[17] Hollerman JJ et al. Gunshot wounds: 2. Radiology. American Journal of Roentgenology. 1990;**155**(4):691-702

[18] Stallings LA et al. Right ventricular bullet embolism: Diagnostic and therapeutic decisions. Injury Extra. 2013;**44**(7):64-66

[19] Greaves N. Gunshot bullet embolus with pellet migration from the left brachiocephalic vein to the right ventricle: A case report. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. 2010;**18**(1):36

[20] Kuo AH et al. Systematic review of civilian intravascular ballistic embolism

reports during the last 30 years. Journal of Vascular Surgery. 2019;**70**(1):298-306

[21] Miller KR et al. The evolving management of venous bullet emboli: A case series and literature review. Injury. 2011;**42**(5):441-446

[22] Hassan AM et al. Pulmonary bullet embolism—A safe treatment strategy of a potentially fatal injury: A case report. Patient Safety in Surgery. 2009;**3**(1):12

[23] Schwoerer AP, Omoshoro-Jones JA, Zellweger R. A bullet embolism to the right popliteal artery following an abdominal gunshot wound. European Journal of Trauma. 2004;**30**(5):319-322

[24] Fernandez-Ranvier GG et al. Pulmonary artery bullet embolism—Case report and review. International Journal of Surgery Case Reports. 2013;**4**(5):521-523

[25] Aoun T, Amine F, Ziad K. Femoral artery embolization of a thoracic stray bullet. Journal of Vascular Surgery Cases and Innovative Techniques. 2017;**3**(3):123-125

[26] Barnes FC, Woodard WT. Cartridges of the World. 15th ed. Stevens Point, Wisconsin, USA: Krause Publishing; 2016

[27] Huang J et al. Popliteal artery embolism of bullet after abdominal gunshot wound. Radiology Case Reports. 2016;**11**(4):282-286

[28] Pan GZ et al. Bullet embolization from an aorto-caval fistula to the heart. Interactive Cardiovascular and Thoracic Surgery. 2013;**16**(5):710-711

[29] Springer J, Newman W, McGoey R. Intravascular bullet embolism to the right atrium. Journal of Forensic Sciences. 2011;**56**:S259-S262

[30] Schroeder ME et al. Retrograde migration and endovascular retrieval of a venous bullet embolus. Journal of Vascular Surgery. 2011;**53**(4):1113-1115

[31] Ettinger J et al. Cardiac bullet embolus after thoracic vena cava penetrating injury causing tricuspid valve insufficiency. International Journal of Surgery. 2007;**5**(1):66-68

[32] Manganas C et al. Traumatic pulmonary arteriovenous malformation presenting with massive hemoptysis 30 years after penetrating chest injury. The Annals of Thoracic Surgery. 2003;**76**(3):942-944

[33] Elison RMA et al. Surgical management of late bullet embolization from the abdomen to the right ventricle: Case report. International Journal of Surgery Case Reports. 2017;**39**:317-320

[34] Decker HR. Foreign bodies in the heart and pericardium: Should they be removed? Journal of Thoracic Surgery. 1939;**9**:62-79

[35] Harken DE, Zoll PM. Foreign bodies in and in relation to the thoracic blood vessels and heart; indications for the removal of intracardiac foreign bodies and the behavior of the heart during manipulation. American Heart Journal. 1946;**32**:1-19

[36] Swan H, Forsee JH, Goyette EM. Foreign bodies in the heart; indications for and technic of removal with temporary interruption of cardiac blood flow. Annals of Surgery. 1952;**135**(3):314-323

[37] Cysne E et al. Bullet embolism into the cardiovascular system. Texas Heart Institute Journal. 1982;**9**(1):75-80

[38] Best IM. Transfemoral extraction of an intracardiac bullet embolus. The American Surgeon. 2001;**67**(4):361

[39] Kortbeek JB, Clark JA, Carraway RC. Conservative

management of a pulmonary artery bullet embolism: Case report and review of the literature. The Journal of Trauma. 1992;**33**(6):906-908

[40] Shannon FL et al. Venous bullet embolism: Rationale for mandatory extraction. The Journal of Trauma. 1987;**27**(10):1118-1122

[41] Wales L, Jenkins DP, Smith PL. Delayed presentation of right ventricular bullet embolus. The Annals of Thoracic Surgery. 2001;**72**(2):619-620

[42] Norton JR et al. Bullet embolus to the right ventricle: Report of three cases. The American Journal of Surgery. 1971;**122**(5):584-590

[43] Ghanaat M et al. Endovascular management of an intracardiac bullet. Injury. 2015;**46**(1):166-168

[44] Yang F-S et al. Non-surgical retrieval of intravascular foreign body: Experience of 12 cases. European Journal of Radiology. 1994;**18**(1):1-5

[45] Nagy KK et al. Missile embolization revisited: A rationale for selective management. The American Surgeon. 1994;**60**(12):975-979

[46] Khanna A, Drugas GT. Air gun pellet embolization to the right heart: Case report and review of the literature. The Journal of Trauma. 2003;**54**(6):1239-1241

[47] Hartzler GO. Percutaneous transvenous removal of a bullet embolus to the right ventricle. The Journal of Thoracic and Cardiovascular Surgery. 1980;**80**(1):153-155

[48] Nolan T et al. Bullet embolization: Multidisciplinary approach by interventional radiology and surgery. Seminars in Interventional Radiology. 2012;**29**(3):192-196

[49] Kaushik VS, Mandal AK. Non-surgical retrieval of a bullet embolus from the right heart. Catheterization and Cardiovascular Interventions. 1999;**47**(1):55-57

[50] Dato GMA et al. Posttraumatic and iatrogenic foreign bodies in the heart: Report of fourteen cases and review of the literature. The Journal of Thoracic and Cardiovascular Surgery. 2003;**126**(2):408-414

[51] Padula RT, Sandler SC, Camishion R. Delayed bullet embolization to the heart following abdominal gunshot wound. Annals of Surgery. 1969;**169**(4):599

[52] Symbas PN, Harlaftis N. Bullet emboli in the pulmonary and systemic arteries. Annals of Surgery. 1977;**185**(3):318

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In the realm of medical practice, the word "embolism" has many implications to many people, with most providers instinctively placing this word within an inherently negative context. Derived from the Greek word, ἐμβολισμός, this term most literally means "interposition." Yet, regardless of how benign this etymological derivation may appear, the clinical context is quite the opposite—a symbol of much dreaded morbidity and mortality. Whether the embolus consists of a blood clot, a fat globule, a bubble of gas, amniotic fluid, or even an iatrogenic or traumatic foreign body, the unfavorable connotations persist even if the patient has few or no associated symptoms and requires no intervention.The primary goal of this book is to provide the reader with an overview of the most common types of embolic phenomena encountered in clinical practice, including some of the key related diagnostic and therapeutic considerations. Among chapters featured in the current collection are important contributions in the areas of pulmonary embolism, fat embolism, embolic complications of non-malignant cardiac tumors, acute arterial embolism of the lower extremity, thrombophilia in pregnancy, bullet and shrapnel embolization, coronary artery embolization, as well as a comprehensive review of venous interventions utilized in the management of thromboembolic disorders. When measured in terms of both human and financial costs, broadly defined "embolic phenomena" have tremendous impact on healthcare systems and societies around the globe. Through this academic effort of both our editorial team and individual chapter authors, we hope to provide the reader with valuable insight into the gravity of the collective problem. Among key takeaway messages of this book is that diagnostic relativity and uncertainty continue to prevail in the realm of "embolic diseases." Consequently, much more progress is required before we are able to declare success.

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