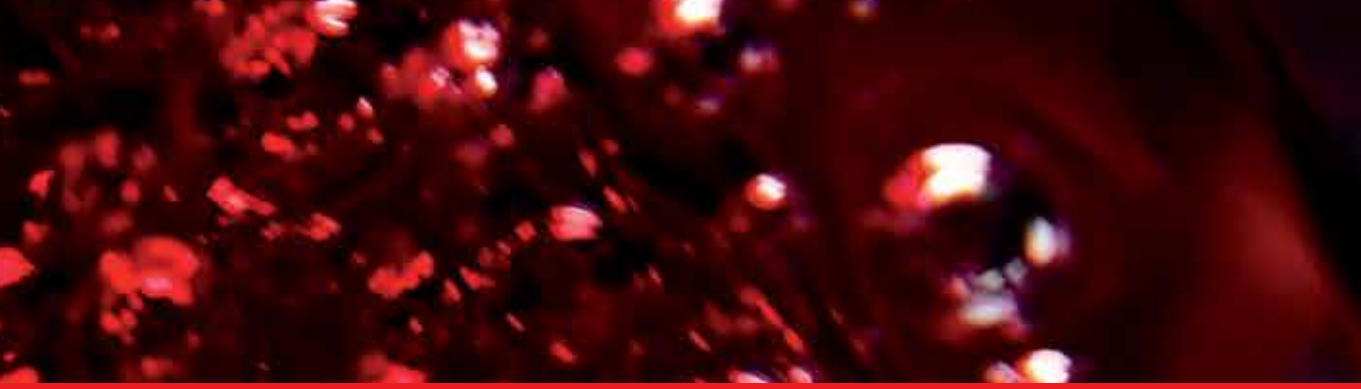

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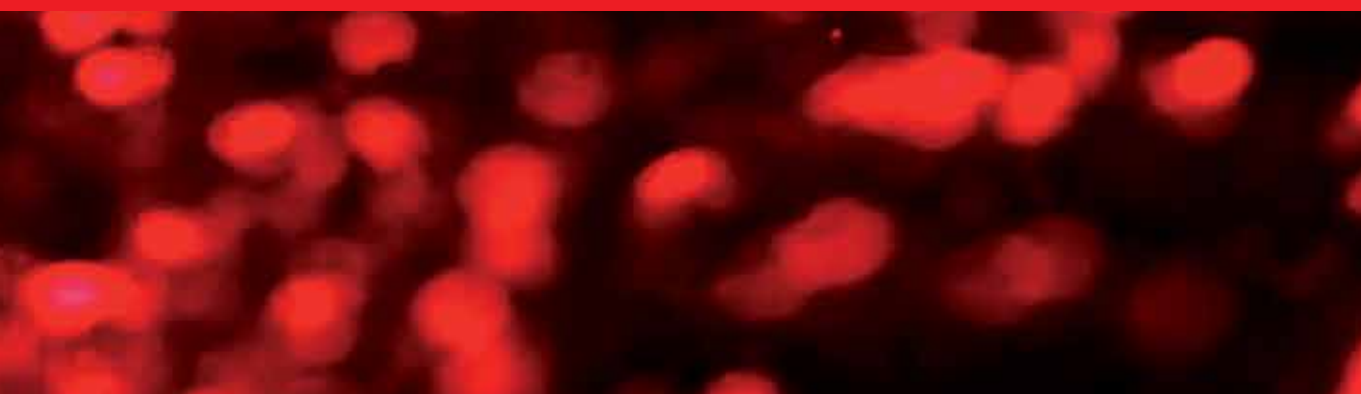
Blood Pressure

From Bench to Bed

Edited by Aise Seda Artis



BLOOD PRESSURE - FROM BENCH TO BED

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Preface

Despite the increasing awareness of healthy habits and changing lifestyles, blood pressure (BP) control keeps its importance for modern humans. Globally hypertension is one of the most important preventable causes of death. It accounts for more than 12.8% of all deaths per year. Also heritable risk factors contribute to elevated BP levels. More than 314 genetic variants are known to affect BP levels. However, adherence to a healthy lifestyle is associated with lower BP regardless of the underlying BP genetic risk [1], [2].

BP is a continuous variable that fluctuates constantly in response to various changes. It shows spontaneous oscillations over short- and long-term periods. There is strong evidence to confirm that increased BP variability is independently associated with higher risk of target-organ damage, cardiovascular events, and mortality [3].

Although hypotension gets less emphasis when the blood pressure is the subject, this doesn't trivialize it. The most common causes of low blood pressure are dehydration or decreased cardiac output. Inadequate perfusion due to low blood pressure causes organ dysfunction due to ischemic damage. Urine output, which normally should not drop below 20 to 30 ml/hr, is a helpful indicator of vital organ perfusion. The earliest clinical manifestation of low blood pressure may be fatigue or shortness of breath on exertion. Then due to poor perfusion, renal failure with wide-ranging metabolic consequences or declining mental status, lethargy, somnolence, and even coma can be seen. The American Heart Association (AHA) does not see low blood pressure as a problem, as long as a person does not experience symptoms.

The cardiovascular and mortality benefits of BP reduction have been well established through many clinical outcome studies. It is widely understood that high BP increases cardiovascular disease (CVD) events, renal failure, and retinopathy. The most recent comprehensive, evidence-based guideline on the prevention, detection, evaluation, and management of high BP in adults was released in 2017 by the American College of Cardiology (ACC) and the American Heart Association (AHA). It suggests several changes, especially in BP classification, the threshold for drug therapy initiation, and the target BP. However, the most appropriate BP goal still continues to be a subject of debate. The American Academy of Family Physicians (AAFP) declined to endorse the ACC/AHA guidelines. AAFP still supports the 2014 report by the panel members appointed to the Eighth Joint National Committee (JNC 8) by the National Heart Lung and Blood Institute (NHLBI). The lower BP goals advised in the last guideline are supported by substantial new high-quality evidence that was not available at the time of the JNC 8 report. However, to attain these goals, greater emphasis will be needed on utilizing team-based care, health information technology including electronic medical records and telehealth, performance measures, quality improvement strategies, and

financial incentives [4]. Elevated BP is one of the major modifiable contributing factors to cardiovascular risk; however, there is often uncertainty as to the "true underlying BP", as patients often present with discrepant BP readings. The BP measurement technique in daily clinical practice is frequently suboptimal, most commonly resulting in falsely elevated readings [4]. This turns the diagnosing and prescribing treatments for patients correctly into a challenge. It is critically important to make sure that an appropriate BP measurement technique is used in order to avoid inappropriate treatment.

Although more of the US population is categorized as hypertensive according to the new guideline (46% now vs 32% before), only 1.9% more require drug therapy. The vast majority of the newly classified patients require only primary prevention with only lifestyle modification. Adherence to a healthy lifestyle (including healthy diet, limited alcohol consumption, low urinary sodium excretion, low body mass index, and increased physical activity) is associated with lower blood pressure regardless of the underlying blood pressure genetic risk [5].

There is a still growing focus on improving BP control. Although the link between salt and blood pressure has already been established, there is heterogeneity in the BP responses to changes in sodium intake. Those individuals in whom none or low salt intake causes large changes in arterial blood pressure, are called salt sensitive, whereas those in whom this leads to the least change are termed salt-resistant [6]. Emerging views support that renal vasodysfunction (not natriuretic dysfunction) is usually a critical factor initiating salt-induced hypertension [7]. Besides Guyton's classical theory of the pressure-natriuresis phenomenon and the role of different protein sodium transporters of the renal tubules; new theories indicate the possible role of the immune system and the existence of a third sodium store in the body [6].

Environmental air pollution seems to be associated with increased pulmonary vascular tonus; meaning longer exposure would impair the right ventricular systolic function. Exercising and having obstructive sleep apnea (OSA) increase the cardiovascular risk due to the pollution [8]. There is an already known vicious cycle between the blood pressure and OSA [9], [10]. It is common and is associated with many vascular risk factors e.g. hypertension, albuminuria, dyslipidemia, insulin resistance, increased inflammation and endothelial dysfunction. OSA has also been shown to be associated with chronic kidney disease and peripheral neuropathy [10]. Peripheral neuropathies, including diabetic neuropathy, are also linked to the blood pressure regulation [11], [12].

As it is a popular topic, a growing body of literature supports a role for the gut microbiota in the development and maintenance of high blood-pressure levels. On the other hand, high dietary intake of fruit, vegetables, and fiber is associated with lower blood pressure levels. Short-chain fatty acids released by the fermentation of fiber by the gut microbiota are linked to lower BP levels in experimental models of hypertension. The composition of human gut microbiota in the setting of high BP levels should be assessed to determine the complex nature of essential hypertension, given that gut microbiota can interact with the host's environment and genome [13], [14].

Amongst many factors prenatal effects are important determinants of our future blood pressure regulation. Maternal de novo hypertension during pregnancy is associated with offspring's elevated BP level in adolescence [15].

The importance of the interactive effects of blood pressure shifts in different clinical conditions is well understood. Interest in the hypertension population that is resistant to medical therapy has been also renewed with emerging device-based therapies for hypertension [16]. Crucial BP control, particularly in certain subpopulations of individuals with hypertension, and the exact mechanisms involved are still debated. The present book aims to cover BP from its measurement to various factors if its control with valuable contributions from different authors, in the light of contemporary data, from bench to bed.

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Chapter 1

The Noninvasive Measurement of Central Aortic Blood Pressure Waveform

Yang Yao, Lu Wang, Liling Hao, Lisheng Xu,
Shuran Zhou and Wenyan Liu

Additional information is available at the end of the chapter

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Abstract

Central aortic pressure (CAP) is a potential surrogate of brachial blood pressure in both clinical practice and routine health screening. It directly reflects the status of the central aorta. Noninvasive measurement of CAP becomes a crucial technique of great interest. There have been advances in recent years, including the proposal of novel methods and commercialization of several instruments. This chapter briefly introduces the clinical importance of CAP and the theoretical basis for the generation of CAP in the first and second sections. The third section describes and discusses the measurement of peripheral blood pressure waveforms, which is employed to estimate CAP. We then review the proposed methods for the measurement of CAP. The calibration of blood pressure waveforms is discussed in the fourth section. After a brief discussion of the technical limitations, we give suggestions for perspectives and future challenges.

Keywords: central aortic blood pressure, generalized transfer function, second systolic pressure, N-point moving average, adaptive transfer function, blind system identification, calibration

1. Introduction

For a long time, central aortic pressure (CAP) and brachial artery pressure were considered the same by clinicians. However, blood pressures in the proximal aorta and brachial artery are different due to wave reflection, the systolic blood pressure (SBP), and pulse pressure (BP) increase from the aorta to periphery, while diastolic blood pressure (DBP) and mean artery pressure (MAP) just decrease 1–2 mmHg toward the peripheral arteries [1–3].

CAP is a better indicator of central hemodynamic stress that is propagated to the peripheral vasculature and target organs, such as the brain and kidneys [4]. Peripheral vasculature and target organs are directly exposed to CAP instead of brachial blood pressure. Measurement of CAP can provide more clinically useful information about cardiovascular system beyond brachial blood pressure. First, recent evidence suggested that CAP may be more strongly related to cardiovascular outcomes [5–15]. For example, central pressure has been shown to have a closer correlation with surrogate measures of cardiovascular disease [6]. Second, CAP responds differently to certain drugs from brachial blood pressure [16–18]. For example, Conduit Artery Function Evaluation (CAFE) which is frequently cited as an example of differential effects of interventions on central and peripheral pressure [16] demonstrated that CAP provides a superior measure of hemodynamic load on the heart and central organs. Besides hypertension, CAP also provides insights into the prevention, diagnosis, and treatment of cardiovascular diseases including coronary artery disease, stroke, myocardial infarction, and heart failure.

Invasive measurement of CAP is considered the "gold standard," while this method is unsuitable for use in routine screening of large populations or clinical diagnosis. In recent years, there is increasing interest in noninvasive measurement of CAP, evidenced by multiple methods proposed and more and more devices commercialized. This chapter discussed current methodologies and devices for CAP estimation.

2. Pulse wave reflection

The arterial tree is made up of dispensable tubes, which transfers the blood from the heart to the periphery. Along these tubes, blood pressure wave, generated by the heart, transmits to the periphery (forward wave) and is reflected back (reflected/backward wave). At different sites along the arterial tree, the forward and reflected waves meet at different times of a cardiac cycle, forming different blood pressure waveforms. This explains the difference in pulse wave contour along the arterial tree. The determinant of the time when the forward and reflected waves meet is the pulse wave velocity (the speed at which the pressure wave transmits in arterial tube). Pulse wave velocity is determined by arterial stiffness, which does not change much in brachial artery with aging or among subjects. This lays the theoretical foundation of using generalized transfer function to estimate aortic pulse wave from radial/brachial pulse wave. Whereas, it does change in central arteries with aging, hypertension, and exercise among subjects, which leads many researchers to seek accurate and practicable adaptive or individualized methods to estimate CAP.

3. Methods of pressure wave recording

3.1. Applanation tonometry

Applanation tonometry was applied to the measurement of arterial pressure waveforms and has been used ever since. It flattens the arterial wall with a flat pressure sensor, eliminating

the tangential pressures and exposing the sensor to the pressure within the artery [19]. The most widely used device employing this method is the Millar applanation tonometry (Millar Instruments, USA). The applanation tonometry is feasible to accurately record pressure waveforms in the radial artery and carotid artery.

A device using arrayed sensors was used [20–23] and commercialized by Nippon Colin and Omron health statistics companies. The device records all the pressure waveforms detected by the sensors and automatically selects the one with the highest quality. This automatic method makes the ubiquitous measurement of radial blood pressure waveform and estimation of CAP possible. The fixed sensor can reduce the effect of movement produced by the operator, less depending on the operator's skill. In these two cases, the recording is more or less related to the operator's skill, and a reproducibility study is essential for each operator in order to guarantee the measurement quality. The watch-type tonometer developed by BPro (HealthSTATS, Singapore) is expected to enable ambulatory tonometric pressure monitoring.

Note that the pressure measured noninvasively using an applanation tonometry is not identical to that invasively measured. The pressure applied to flatten the arterial wall and compress overlying tissues should be taken into account. The tonometric pressure wave should be calibrated using brachial arterial pressures.

3.2. Brachial cuff-based measurements

More recently, a number of brachial cuff-based devices have appeared to assess CAP. Mobil-O-Graph (I.E.M. GmbH, Germany), Vicorder (Skidmore Medical Ltd., UK), WatchBP (Microlife Corp, Taiwan, China), and BPLab (Petr Telegin, Russia) estimate CAP from the ordinary oscillometric pulse volume recording (diastolic oscillometry) data. In some devices, such as DynaPulse (Pulse Metric Inc., USA), Arteriograph (TensioMed Ltd., Hungary), and BP+ (Uscom Ltd., Australia), supra-systolic brachial cuff plethysmography is used to acquire supra-systolic recordings to estimate CAP. Supra-systolic recordings of oscillometric pulse waveform are made with a cuff pressure above SBP so that the brachial artery is totally occluded. SphygmoCor XCEL and Oscar 2 with SphygmoCor record the blood pressure waveform under sub-diastolic blood pressure. Some devices may offer the advantage of acquiring CAP, ambulatory blood pressure monitoring (ABPM), as well as ambulatory assessment of CAP which may further improve risk stratification. Although some validation studies have been reported, the theoretical validity of the use of a simple cuff as a pressure sensor is not fully understood. Moreover, demonstrative clinical data supporting its accuracy seem to be inadequate. Therefore, the clinical validity of such devices should be evaluated in the future before being used as a clinical tool.

4. Methods for central pressure estimation

The invasive method directly records the blood pressure waveform in the ascending aorta using a pressure-sensing catheter during cardiac catheterization. This method can continuously provide accurate blood pressure waveform and is considered the "gold standard." However, the invasive method is only applicable during catheterization, not appropriate for

routine high-throughput screening of CAP. Recently since the 1990s, noninvasive methods have been introduced and validated for the assessment of central blood pressure. An overview of the related commercial devices is described in **Table 1**.

4.1. Direct method (simple substitution)

Pressure waveforms in the ascending aorta and carotid artery are similar. Carotid pressure is often used as a surrogate measure for CAP [24, 25]. This method directly measures pressure waveform in common carotid artery by applanation tonometry and calibrates the waveform by the mean and diastolic pressure (being identical to that in brachial artery). PulsePen (DiaTecne s.r.l., Italy), Complior Analyze (Alam Medical, France), and NIHem (Cardiovascular Engineering Inc., USA) employ this method.

Despite the similarity of the aortic and carotid pulse wave, the amplitude of the augmented pressure wave in the ascending aorta is much higher than that in the carotid artery [19], which affects the calculation accuracy of some cardiovascular parameters like the augmentation index (AI).

4.2. Generalized transfer function (GTF)

This approach assumes that the relationship between central aortic and brachial/radial blood pressure waveforms keeps the same among all subjects (or a set of subjects with similar physiological and pathological characteristics). This relationship is modeled by a generalized transfer function. This generalized transfer function is employed to reconstruct the central pressure waveform from brachial or radial pressure waveform [26, 27]. This is the most well validated [28] and the most widely used method so far. **Figure 1** demonstrates the generalized transfer function produced from 26 subjects. The transfer function is a low-pass filter that compensates for the boost in high frequency components of the pressure waveform as it travels from central aorta to the periphery. This method can provide not only quantitative CAP but also central aortic pressure waveform, allowing further analysis to access more cardiovascular parameters and predict cardiovascular status. The GTF method was first embedded in SphygmoCor (AtCor Medical, Australia), the first device accepted by US Food and Drug Administration (FDA) for the estimation of CAP.

The CAP determined by the GTF method is highly correlated with the brachial pressure used for calibration. Input errors of GTF-brachial pressure values result in a quantifiable effect on its output-CAP. The transfer error by the GTF depends on heart rate and BP levels, which should be taken into account when applying GTF to populations with different hemodynamic conditions [30].

The validity of the GTF method in estimating central arterial pressures was evaluated [28]. The generalizability of GTF has been questioned [31], especially in some special hemodynamic conditions (chronic kidney disease or arterial stiffness) [32]. In addition, not all methods that generate GTFs are equally accurate [33].

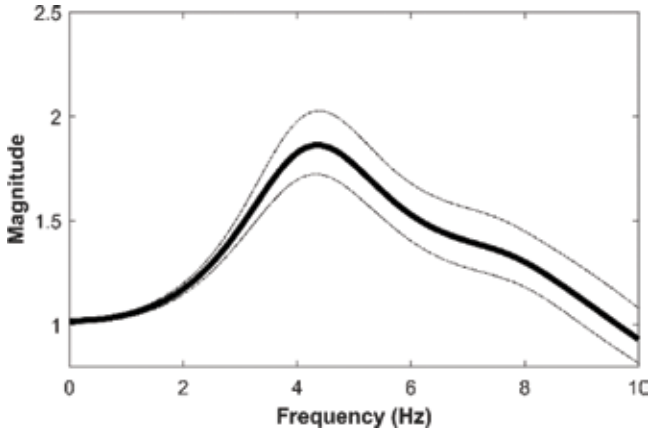

Figure 1. Frequency response of GTF produced from 26 subjects (the area between the dash-dot lines is the 95% confidence interval) [29].

4.3. Second systolic pressure of periphery (SBP2)

Central SBP can be estimated directly from the properly calibrated brachial or radial pressure waveform. The evidences indicate that the reflected wave peak recorded in the periphery approximates to central SBP, since pressure gradients in the arterial system are relatively small during late systole and the late systolic shoulder represents the dominant peak in most adults from midlife onward [34, 35]. Therefore, for older adults, central aortic systolic blood pressure can be calculated [28] via a regression equation employing the second systolic peak as an independent variable [36, 37]. The method is used by Omron HEM-9000AI (Omron Healthcare, Japan), which records the radial pressure waveforms by tonometry, Arteriograph and WatchBP, which calculate central SBP from the brachial cuff pressure.

One drawback of this method is that it does not work when the second peak of a brachial/radial pressure waveform disappears (which often happens in the old or in patients with hypertension or arterial stiffness). The performance of this method in estimating CAP depends on the morphology of brachial/radial pressure waveform [38]. For example, central aortic SBP may be inaccurate in younger individuals with early, non-augmented peak systolic pressure [39]. Besides, this method also suffers the calibration error.

4.4. N-point moving average (NPMA)

As mentioned above, the GTF method can be regarded as applying a low-pass filter to the brachial/radial pressure waveform. A simplified approach for assessing CAP is the N-point moving average (NPMA) method, which is a kind of first-order low-pass filter, removing all higher frequency-related pulse wave features, which are typically related to wave reflections,

and, therefore, providing only central aortic SBP instead of aortic blood pressure waveform. This method is also a generalized method as the GTF method does; it suffers the intersubject and intra-subject variability. The accuracy of NPMA cannot be superior to that of GTF method. This method is embedded in BPro device and A-Pulse CASP application software (HealthSTATS, Singapore). It does not provide an estimated central aortic blood pressure waveform.

4.5. Adaptive transfer function (ATF)

The fundamental assumption of the GTF method is that the relationship between central aortic and the peripheral pulse waves remains the same in different subjects or in different status of one subject, while, as mentioned before, central arterial stiffness differs with aging, hypertension, or exercise, which changes the relationship between central aortic and brachial/radial pressure waves. Several adaptive transfer function methods were proposed trying to tune the generalized transfer function and derive more reliable CAP [29, 40].

For example, in our previous work, using aortic and brachial pulse waves derived from 26 patients who underwent cardiac catheterization, generalized transfer functions (GTF) were derived based on the autoregressive exogenous model. Then for each individual, the GTF was tuned by its peak resonance frequency, as shown in **Figure 2**. The optional peak resonance frequency for an individual was determined by regression formulas using brachial systolic blood pressure. Another work by Swamy [40] used similar method and validated the method in dogs during multiple interventions.

4.6. Individualized transfer function (ITF)

The GTF method does not account for intersubject or intra-subject variability of the transfer function. Individualized or quasi-individualized methods were proposed in recent years [41–43]. These methods primarily employ a physical transmission line model and focus on the individualization of pulse transit time, which is the main determinant of the aorta-brachial and aorta-radial model. Till now, none of the ITF methods are fully validated by invasive data and unfortunately rarely used in clinical practice [44].

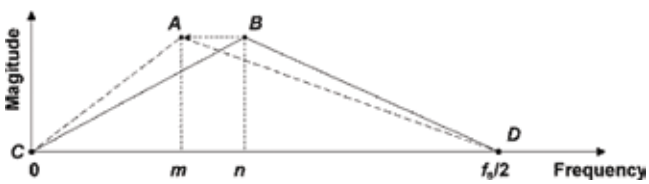

Figure 2. Diagram of adaptively adjusting the GTF to the desired ATF. The solid line indicates the GTF, and the dotted line indicates the desired ATF. A and B indicate the peaks of the desired ATF and GTF, respectively. M and n are the peak resonance frequencies of the desired ATF and the GTF, respectively [29].

4.7. Blind system identification (BSI)

The blind system identification (BSI) method reconstructs the input from two or more outputs. In the estimation of central aortic pressure waveform, BSI reconstructs the central aortic pressure waveform based on two peripheral pressure waveforms [45–50]. This method is fully individualized, without the need of measuring or estimating pulse transit time. The main drawback of this method is that it requires extra measurement of peripheral pressure waveforms. The two aorta-periphery models should not be similar in order to provide enough information, which added the inconvenience of clinical application.

5. Calibration

The tonometry waveforms in carotid artery are calibrated to MAP and DBP which are similar throughout the arterial system, whereas SBP varies from the proximal artery to the periphery [1–3]. The calibration of tonometry waveforms in carotid artery are calibrated to brachial SBP and DBP. Because of variable amplification of the pressure waveform as it travels from the brachial to the radial recording site, the calibration of the radial waveform with brachial SBP and DBP leads to neglect of brachial-to-radial amplification, which may be sufficiently high to be of practical importance [51–54]. This results in underestimation of radial systolic, mean, and pulse pressure, whereas diastolic pressure is comparable between brachial and radial sites [53, 55]. Since the radial waveform is improperly calibrated, the derived aortic pressure waveform will have systolic, mean, and pulse pressures underestimated. And the difference between central and brachial pressures is overestimated. Thus, incorrect calibration simultaneously underestimates central pressure and overestimates central-to-brachial pressure amplification. In order to decrease calibration errors, the calibration of tonometry waveforms in radial artery with brachial MAP and DBP may be preferable.

The calibration of tonometry waveforms with brachial MAP and DBP also has errors. One error is the inexact MAP obtained. Using brachial blood pressure and a formula to estimate brachial mean pressure is not acceptable because of high variation in the form factor of the brachial pressure waveform which can affect the accuracy of calibration. The maximum amplitude algorithm, which is commonly employed in oscillometric devices to estimate mean arterial pressure, is susceptible to errors that are related to arterial stiffness [56–58]. Another error is related to the inaccuracy of brachial cuff blood pressure used to calibrate which will be inevitably transferred to the resulting CAP.

To sum up, all current methods for estimating CAP are critically dependent on concurrent assessment of conventional peripheral blood pressure for calibration. The brachial blood pressure is used as the source of calibration in all the techniques of estimating CAP. The noninvasive oscillometric blood pressure devices are known to underestimate systolic and overestimate brachial diastolic blood pressure [59, 60]. Estimates of central pressure based on these incorrect estimates of brachial blood pressure will be proportionally confounded. The auscultatory blood pressure, which represents the gold standard measure of peripheral blood pressure, also has error similar to the oscillometric device [61].

6. Limitations

6.1. Calibration error

Till now, all the available noninvasive methods and devices suffer the calibration error in the estimation of CAP. This means that the performance of these noninvasive methods largely depends on the measurement of peripheral blood pressures [53, 62]. That is why measurements from various methods or devices vary widely. In studies that performed direct comparisons of existing devices, agreement between devices is suboptimal [59, 63, 64]. New noninvasive methods should be introduced to get rid of calibration error, and the accuracy of peripheral blood pressure measurement should be improved.

6.2. Lack of CAP-based standard diagnostic criteria

Most standard diagnostic criteria for hypertension are based on brachial blood pressures. However, there are no standard diagnostic criteria available based on CAP. Clinicians should consider providing CAP-based standard diagnostic criteria for hypertension and some other cardiovascular risks.

7. Perspectives and future challenges

Central aortic pulse waves contain a vast amount of physiological and pathological information regarding cardiovascular system [65, 66]. Many approaches have been attempted to estimate aortic pressure waveform or CAP noninvasively. However, these techniques are either not fully validated or not accurate enough in estimating CAP compared with the invasive method. Their applications in clinical practice are limited. CAPs derived from different devices are not consistent, making it impossible to substitute for each other clinically. Therefore, these noninvasive methods not only need further improvement but also further clinical validation. There are basically two problems to be solved.

7.1. Getting rid of calibration error

As mentioned above, most of the current noninvasive methods suffer calibration error. Novel methods are required to get rid of the calibration error. And the accuracy of current methods for blood pressure measurement should be improved.

7.2. Individualized model for estimating central pressure waveform

Both the mathematical models and physical models are mostly used to establish an average model and apply it to each individual. The difference between individuals inevitably brings in error. The parameters of mathematical transfer function have no clear physical meaning. It is not easy to individualize them. One thing we can do is to calculate a transfer function for each specific population with similar physiological status (such as the same gender, the same generation, or those with the same diseases). The physical models are built on the basis of the

mechanical properties of cardiovascular system. The parameters included in the models have a clear physical meaning. Some of them are potentially available via direct measurement or estimation. But many of these parameters are not easily available. In recent years, although some researchers have presented individualized methods, they are either not convenient or do not show much improvement compared with GTF methods. Besides, most of them are not fully validated. Novel convenient individualized method with fully validation is recommended.

A. Appendices

Device company	Site of record	Method of waveform recording (Sensor)	Method of estimation	Calibration	Invasive validation/ FDA approval
PulsePen DiaTecne s.r.l., Italy	Carotid artery	Applanation tonometry, Single, manual	Simple substitution	Brachial cuff MAP/DBP	[67]/no
Complior Analyse Alam Medical, France	Carotid artery	Applanation tonometry, Single, fixed	Simple substitution	Brachial cuff MAP/DBP	[68]/no
NIHem Cardiovascular Engineering Inc., USA	Carotid artery	Applanation tonometry, Single, manual	Simple substitution	Brachial cuff MAP/DBP	[69]/no
HEM-9000AI Omron Healthcare, Japan	Radial artery	Applanation tonometry Arrayed [40], fixed	SBP2 + regression	Brachial cuff SBP/DBP	[34, 37, 39, 70]/no
BPro+A-Pulse CASP HealthSTATS, Singapore	Radial artery	Applanation tonometry Single, fixed(watch type)	N-point moving average	Brachial cuff SBP/DBP	[71, 72]/yes
Gaon Hanbyul Meditech, Korea	Radial artery	Applanation tonometry Single, fixed	GTF	Brachial cuff SBP/DBP	[73]/no
SphygmoCor CVMS AtCor Medical, Australia	Radial artery	Applanation tonometry Single, manual	GTF	Brachial cuff SBP /DBP	[27, 28, 62, 70, 71, 74–77]/yes
SphygmoCor XCEL AtCor Medical, Australia	Brachial artery	Sub-diastolic brachial cuff plethysmography	GTF	Brachial cuff SBP/DBP	[78]/yes
Oscar 2 with SphygmoCor SunTech Medical, USA	Brachial artery	Sub-diastolic brachial cuff plethysmography	GTF	Brachial cuff SBP/DBP	Yes/yes

Device company	Site of record	Method of waveform recording (Sensor)	Method of estimation	Calibration	Invasive validation/ FDA approval
cBP301 Centron Diagnostics, UK (acquired by SunTech Medical)	Brachial artery	Brachial cuff plethysmography	GTF	Brachial cuff SBP/DBP	[79]/yes
Mobil-O-Graph I.E.M. GmbH, Germany	Brachial artery	Brachial cuff pulse volume plethysmography	GTF	Brachial cuff SBP/DBP	[74]/yes
Arteriograph TensioMed Ltd., Hungary	Brachial artery	Supra-systolic brachial cuff plethysmography	SBP2 + regression	Brachial cuff MAP/DBP	[80, 81]/no
Vicorder Skidmore Medical Ltd., UK	Brachial artery	Brachial cuff pulse volume plethysmography	GTF	Brachial cuff MAP/DBP	[62, 82]/yes
BPLab Petr Telegin, Russia	Brachial artery	Brachial cuff pulse volume plethysmography	GTF	Brachial cuff SBP/DBP	No/no
BP+ Uscom Ltd., Australia (acquire Pulsecor Ltd., Cardioscope II)	Brachial artery	Supra-systolic brachial cuff plethysmography	Physical model Brachial supra-systolic waveform	Brachial cuff SBP/DBP	[83]/no
DynaPulse Pulse Metric Inc., USA	Brachial artery	Supra-systolic brachial cuff plethysmography	Physical model	Brachial cuff SBP/DBP	Yes/yes
WatchBP Microlife Corp, Taiwan, China	Brachial artery	Brachial cuff pulse volume plethysmography	(SBP2, DBP, As, Ad) + regression	Brachial cuff SBP/DBP	[84, 85]/yes
ARCsolver+ VaSera VS-1500 Austrian Institute of Technology, Austria	Brachial artery	Brachial cuff pulse volume plethysmography	GTF	Brachial cuff SBP/DBP	Yes/yes

As, area under systolic pressure trace; Ad, area under diastolic pressure trace.

Table 1. Statistics and comparison of noninvasive CAP measuring device.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 2

Outdoor Air Pollution and Arterial Hypertension

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Additional information is available at the end of the chapter

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Abstract

Air pollution is a major environmental risk factor. There is accumulating evidence that air pollution could induce elevated blood pressure and potentiate hypertension. Acute elevations in the outdoor air pollution levels can trigger immediate or shortly delayed increases in arterial blood pressure. Moreover, few studies suggest that short-term increases in the levels of particulate and gaseous pollutants could lead to an acute onset of hypertension. Prolonged exposure to outdoor air pollution is associated with elevated blood pressure. Furthermore, some longitudinal studies have linked long-term exposure to air pollution with the incidence of hypertension. Various components of air pollution, such as inhalable particulate matter ($PM_{2.5}$, PM_{10}), nitrogen oxides, sulfur dioxide, and ozone, have shown associations with blood pressure in some studies. The hypothesized underlying mechanisms include inflammatory reactions and oxidative stress in lungs and in systemic circulation, imbalance of autonomous nervous system, and pathologic changes in vascular endothelium. In addition to "traditional" susceptible groups such as elderly individuals or patients with chronic diseases, children and pregnant women could be especially susceptible to the adverse effects of air pollution. The interplay of air pollution with the related environmental exposures, such as traffic noise and climate change, should be investigated further.

Keywords: ambient air pollution, particulate matter, nitrogen oxides, ozone, sulfur dioxide, cardiovascular effects of air pollution, high blood pressure, hypertension

1. Introduction

Atmospheric air pollution is a major environmental risk factor. It was estimated that outdoor air pollution caused 3 million premature deaths worldwide in 2012 [1]. Air pollution is a

heterogeneous mixture of substances, including particles and gaseous compounds, which are not normal air constituents and can harm living organisms.

Airborne particles, or particulate matter (PM), is a heterogeneous mixture of solid and liquid particles suspended in air [2]. PM is classified by its aerodynamic diameter, ranging from ≤0.1 micrometers (μm), which is comparable to the size of some molecules or smaller viruses, to very large particles of >100 μm at the limit of vision [3]. Particles ≤10 μm in diameter (PM_{10}), called thoracic, or inhalable particles, can be inhaled into lungs, while larger particles do not get past the nasopharynx [3]. Thoracic particles consist of fine, ultrafine, and coarse particles. Fine particles are small thoracic particles with aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$). The ultrafine particles (UFP) are a subfraction of fine PM with a diameter ≤ 0.1 $\mu g/m^3$. Coarse fraction particles include the thoracic particles, larger than $PM_{2.5}$. Smaller particles can be inhaled deeper into the respiratory tract and reach the alveoli. It is also hypothesized that very small particles could directly translocate into the circulation [4]. The chemical composition of the particles varies greatly. The most common constituents are nitrates, sulfates, carbon, organic compounds (such as polycyclic aromatic hydrocarbons), biological compounds (such as bacterial endotoxin and cell fragments), and metals [2]. Both the size and the chemical composition of PM change over time and space [2]. Fuel and biomass combustion produces large amounts of so-called carbonaceous PM, the most important combustion by-products besides carbon dioxide [5]. One of the fractions of the carbonaceous PM, called black carbon (BC), is a commonly used marker of traffic-related emissions.

Gaseous compounds comprise the second major group of air pollutants. Nitrogen oxides, cumulatively referred to as NO_x, consist of nitrogen dioxide (NO_2) and nitrogen monoxide (NO), and a lesser proportion of other nitrogen oxides and nitrogen-containing acids [2]. NO_x originates from fossil fuel combustion in motor vehicles and from industrial processes, such as power generation. It can also be formed naturally, e.g., through bacterial metabolism of nitrogen-containing compounds, from fires, volcano eruptions, etc., but to a lesser extent, than from anthropogenic sources. Tropospheric ozone (O_3) is a highly reactive gaseous secondary pollutant formed in photochemical smog reactions in the presence of sunlight, NO_x, and reactive hydrocarbons. O_3 can be formed from NO_2 by photolysis, producing NO [2]. O_3 can be scavenged by NO, regenerating NO_2 and O_2 [2]. Sulfur dioxide (SO_2) is a highly irritating gas with pungent odor and taste. It originates from power generation and industrial processes including combustion of sulfur-containing fuels in power generation, as well as from diesel car engines, household heating, etc. [2]. The formerly high levels of SO_2 in Western countries have reduced substantially over the past decades, through efficient technologies to remove sulfur from fuel prior to combustion. Similar trend of a rapid decline of the ambient SO_2 levels has been recently observed in China [6]. However, in other regions, such as India, the emission of SO_2 is still growing [6]. SO_2 and NO_x are major precursors for acid rains and secondary particle formation. Other gaseous components of air pollution include carbon dioxide (CO_2) or, in case of incomplete combustion, carbon monoxide (CO), volatile organic compounds (VOCs), and ammonia (NH_3).

Air pollution is an important risk factor for cardiovascular disease. More than a decade ago, the American Heart Association published a statement on the cardiovascular effects of air pollution, concluding that exposure to PM contributes to cardiovascular morbidity and

mortality [2]. Based on the reviewed evidence, the authors concluded that short-term exposure to elevated levels of PM leads to increases in cardiovascular mortality and morbidity, reflected in elevated hospital admissions for cardiopulmonary diseases [2]. Moreover, the longer duration of exposure can reduce overall life expectancy by few years [2]. In the updated review of the literature [7], published few years later, the authors concluded that there is a causal relationship between exposure to $PM_{2.5}$ and cardiovascular morbidity and mortality. The authors emphasized that acute exposure to $PM_{2.5}$ over a few hours to weeks can trigger cardiovascular disease–related mortality and nonfatal events, while long-term exposure (over months or years) contributes to a higher cardiovascular mortality and reduced life expectancy [7]. It is also hypothesized that long-term exposure to air pollution may have a greater effect on cardiovascular disease than the short-term exposure [7].

There is a growing interest to the effect of air pollution on traditional cardiovascular risk factors, such as hyperglycemia, dyslipidemia, and high blood pressure (BP). On one hand, the individuals with these risk factors might be particularly vulnerable to adverse cardiovascular effects of air pollution [7]. On the other hand, air pollution exposure could potentiate the development of these risk factors; thus, they could act as mediators of the adverse effect of air pollution on CVD [7].

High BP is, alongside air pollution, one of the top five risk factors for mortality and disability worldwide [8]. According to the recent Global Burden of Disease Study, 10.4 million deaths and 208.1 million disability adjusted life years were attributed to high systolic BP in 2013 globally [8]. It was estimated that in adults aged 40–69 years, an increase in systolic BP by 20 mmHg or in diastolic BP by 10 mmHg was associated with a twofold or an even higher difference in death rate from vascular events, such as ischemic heart disease or stroke [9]. Even a relatively small reduction in BP is associated with substantial health benefits. For example, a decrease in the systolic BP by 2 mmHg can reduce stroke mortality by 5%, coronary heart disease (CHD) mortality by 4%, and total mortality by 3% [10]. The same reduction in diastolic BP was associated with a 6% decrease in the risk of coronary heart disease and 15% reduction in the risk of stroke and transient ischemic attack [11]. A factor with a relatively small impact on BP, but affecting the large proportion of the population, is therefore of high importance for public health.

There is evidence that air pollution could induce elevated blood pressure and potentiate hypertension [3]. Short- and long-term elevations in outdoor $PM_{2.5}$ have been linked to higher BP, hypertension, and a raise in emergency visits for hypertension to hospitals [12]. Different components of air pollution, such as gases, larger or smaller particles, carrying various chemical substances on their surface, could be responsible for blood pressure elevation. Inflammatory and pro-oxidative reactions, triggered by pollutants in lungs and later in systemic circulation, imbalance of autonomous nervous system, and pathologic changes in vascular endothelium could be underlying pathways of this elevation. Despite extensive research in the past decades, the evidence is still quite heterogenic with regard to the study methods, population characteristics, pollutants' assessment and composition, research questions, etc. We aim to provide a comprehensive review of the available literature on the evidence of short- and long-term effects of air pollution on BP and hypertension in the general population and susceptible population groups, discuss pathophysiologic mechanisms, which could be responsible for the prohypertensive effect of air pollution, and consider related environmental factors.

2. Short-term effects of air pollution

A growing number of studies have investigated the short-term effects of ambient air pollutants on blood pressure and hypertension. We identified 30 studies on short-term associations of air pollution with BP or hypertension, performed in healthy volunteers or in general population [13–42]. Sixteen studies were conducted in North America [14, 16–19, 21, 22, 24, 25, 32, 34, 36–39, 43], four studies were conducted in South America [13, 23, 35, 41], four studies took place in Europe [28–31], and six studies were performed in Asia [15, 20, 26, 27, 40, 42]. While the vast majority of the publications have focused on acute changes in BP [14–25, 28, 31–35, 37–39, 42, 44], five studies have investigated hypertension as outcome [13, 26, 27, 36, 41], and one study has included both BP and hypertension [29]. Consistent with the previous reviews [7, 12], we found that in most of the investigated studies a transient increase in BP following short-term exposure to air pollution or some of its components was observed. Here, we briefly summarize the observed results by the type of the respective air pollutant.

2.1. Black carbon (soot)

Short-term associations of BC with BP were investigated in five studies [31, 32, 34, 38, 39]. Four of them reported positive associations with BP [31, 32, 34, 45], while one study found no associations [38]. The exposure duration ranged from very acute (2 hours) to a longer period (7 days). A controlled two-hour exposure to BC from traffic was positively associated with postexposure elevation in systolic BP (1.22 mmHg (95% confidence interval (CI): 0.28, 2.17) per interquartile range) [31]. In a panel study with 28 nonsmoking seniors, 24-hour mean BC was positively associated with systolic (estimated increase of 3.2 mmHg (standard error (SE) 1.46 mmHg) per 487 ng/m^3 BC) and diastolic (4.32 mmHg (1.33)) BP [32]. Weekly average BC concentration was associated with increased BP in a cohort of 461 elderly men: per increase in BC by 0.43 μg/m^3, the estimated increase in systolic BP was 1.46 mmHg (95% CI: 0.10, 2.82), and the estimated increase in diastolic BP was 0.87 mmHg (95% CI: 0.15, 1.59) [34]. Similar positive associations were reported in a reanalysis of this cohort with a larger sample of 789 elderly men [39]. No study has investigated the short-term associations of soot with hypertension.

2.2. Coarse particles: PM_{10}, total suspended particles (TSP)

In total, 12 studies investigated the association of short-term PM_{10} with BP and hypertension [15, 16, 18–20, 23, 27, 28, 31, 35, 36, 42]. Nine of them observed positive associations [15, 16, 18–20, 27, 31, 35, 36]. For example, in a study with 120 healthy volunteers, a 10 μg/m^3 increase in 8-day ambient PM_{10} was associated with an increase in systolic BP by 0.98 mmHg (95% CI: 0.34, 1.61) and an increase in diastolic BP by 0.71 mmHg (95% CI: 0.18, 1.24) [15]. Similarly, increased systolic and diastolic BP were observed in few controlled exposure studies with healthy volunteers, following short-term exposure to coarse concentrated ambient particles (CAPs) [16, 18, 19].

Few studies observed positive associations of short-term PM_{10} elevations with hypertension: for example, a 10 μg/m^3 increase in ambient PM_{10} was associated with an odds ratio (OR) of

1.060 (95% CI: 1.020, 1.101) for hospital admissions for hypertension in China [27]. A similar effect estimate was reported in a comparable study in Canada [36].

Two studies assessed coarse PM exposure as total suspended particles (TSP) [13, 29]. This measure stands for the fraction of particles with diameters <50–100 μm and could be seen as a crude surrogate for PM_{10}. In a study with 2607 adults from a population-based MONICA cohort in Germany, 24-hour and 5-day mean TSP was positively associated with systolic BP: for example, an increase by 70 $\mu g/m^3$ in the 5-day mean TSP was associated in an increase in systolic BP by 1.96 mmHg (95% CI: 0.75, 3.15) [29]. The authors also observed a weaker positive relationship with diastolic BP and a positive association with hypertension: OR 1.63 (95% CI: 1.21, 2.20). [29]. Similarly, in an ecological time-series study in Brazil, TSP generated from sugarcane burning was associated with an increase in hypertension-related hospital admissions [13].

Interestingly, two studies with the same professional group (traffic controllers) from Brazil reported divergent results: one study observed an acute increase in systolic and diastolic BP [35], while another study reported no associations with PM_{10} [23]. A study with 2612 elderly subjects in France reported an inverse association of ambient PM_{10} with systolic BP: an increase in PM_{10} during the fifth lag hour by 10 $\mu g/m^3$ was associated with a decrease in systolic BP by 1.12 mmHg (95% CI: −1.90; −0.30) [28]. Similarly, inverse associations of 1- to 3-day lag PM_{10} with systolic BP and pulse pressure were observed in a large population-based study in Taiwan (N = 9238) [42].

2.3. Fine and ultrafine PM

The short-term associations of ambient fine particles ($PM_{2.5}$) with BP and hypertension were investigated in 17 studies [14–17, 22, 24, 25, 27, 30, 32–34, 36–38, 40, 41] and overall showed more mixed results, than studies with coarse particles. Four studies with healthy volunteers observed positive associations with at least one BP metrics [16, 32, 37, 40]. Moreover, two studies with larger population-based samples observed similar results [14, 24]. An increase in 5-day mean $PM_{2.5}$ by 10 $\mu g/m^3$ was associated with an increased systolic BP (4.7 mmHg, $p = 0.05$) and pulse pressure (4.04 mmHg, $p = 0.03$), and no association was observed with diastolic BP in a random sample of 347 residents of Detroit, USA [24]. Similar results were reported in an analysis with a population-based cohort from six US communities (N = 5112): a 10 $\mu g/m^3$ increase in a 30-day mean $PM_{2.5}$ was associated with an increase in pulse pressure by 1.12 mmHg (95% CI: 0.28, 1.97) [14]. Likewise tendency, though not statistically significant, was found with systolic BP (0.99 mmHg; 95% CI: –0.15, 2.13), while no association was observed with diastolic BP [14].

The associations of short-term exposure to $PM_{2.5}$ with hospital admissions for hypertension were investigated in three studies, all reporting positive findings [27, 36, 41]. A study in Canada found that per increase in 3-day lag $PM_{2.5}$ concentration by 6.2 $\mu g/m^3$ the estimated OR for hospital admissions for hypertension was 1.07 (95% CI: 1.01, 1.11) [36]. Similarly, a study in Brazil reported a positive association of ambient $PM_{2.5}$ with hospital admissions for hypertension: per 10 $\mu g/m^3$ increase in $PM_{2.5}$ lags 0–4, the estimated relative risks (RR) were 1.018–1.021 ($p < 0.05$) [41]. A study in China also reported a very comparable estimate: p OR 1.084 (95% CI: 1.028, 1.139) per 10 $\mu g/m^3$ increase in short-term $PM_{2.5}$ [27]

Some studies report different results by subgroup or by exposure measurement. For example, a positive association of $PM_{2.5}$ CAP exposure with systolic BP was observed in a group of 12 healthy volunteers, while in the group of 12 participants with asthma, this association was inverse [25]. One study observed no association with ambient $PM_{2.5}$ from an urban monitoring station, but found a positive association of personal-level exposure, measured with personal environmental monitors [17]. In another study, the positive association of outdoor $PM_{2.5}$ with systolic BP was observed only in subjects taking antihypertensive medication (N = 57 (65% of the total sample) [30]. No associations with BP were reported in five studies [15, 22, 33, 34, 38].

Only three studies so far have investigated the associations of ultrafine particles (UFP) with acute changes in BP: two of them reported positive associations with systolic BP [31] and pulse pressure [33], while one study found no association [38]. We could not find studies on the association of UFP with hypertension.

2.4. Ozone

Very few studies have investigated the acute effects of gaseous pollutants on BP and hypertension. The effect of short-term O_3 exposure was investigated in four studies so far [20, 33, 38, 42]. In a large population-based cohort from Taiwan (N = 7578), an increase in 3-day O_3 by 12.15 particles per billion (ppb) was associated with an increase in diastolic BP by 0.37 mmHg (95% CI: 0.04, 0.69); no association with systolic BP was found for O_3 [20]. However, in a similarly large cohort from Taiwan (N = 9238), 1- to 3-day lag O_3 was associated with decreased systolic BP and pulse pressure, and not associated with diastolic BP [42]. In a small study with healthy female volunteers from Canada, 3-hour exposure to O_3 was positively associated with both systolic and diastolic BP: the estimated increase per 24 ppb O_3 was 2.49% (95% CI: 0.141, 4.84) and 3.26% (95% CI: 0.012, 6.51) systolic and diastolic, respectively [38]. No association with BP was observed in a controlled exposure study with air pollution from a steel plant [33].

2.5. Nitrogen oxides

The acute effects of nitrogen oxides on BP and hypertension have been investigated in eight studies so far [22, 23, 26, 31, 33, 36, 38, 42]. Positive associations with BP and hypertension were observed in four studies [22, 26, 31, 36]. For example, in a study with 39 healthy volunteers and exposure to air pollution at a bus stop in Canada, an increase in NO_2 by 1 ppb resulted in an increase of systolic BP by 0.44 mmHg ($p < 0.05$) [22]. Similarly, in a study with 28 healthy volunteers in Spain, elevated NO_x was associated with higher systolic BP [31]. Two studies reported short-term associations with quite comparable OR estimates: per increase in NO_2 by 10 $\mu g/m^3$, the estimated OR was 1.101 (95% CI: 1.038, 1.168) in a study from China [26], and per increase in NO_2 by 12.8 ppb, the estimated OR was 1.06 (95% CI: 1.00, 1.12) in a study from Canada [36]. Three studies reported no associations of NO_x with BP [23, 33, 38]. Interestingly, discordant associations with different BP metrics were observed in a large Taiwanese cohort (N = 9238): per 14.9 ppb of NO_2 at lag day 2, diastolic BP increased by 1.15 mmHg (95% CI: 0.56, 1.73), while systolic BP and pulse pressure decreased by 0.87 mmHg (95% CI: −1.74, −0.01) and −1.56 mmHg (95% CI: −2.25, −0.88), respectively [42].

2.6. Sulfur dioxide

The short-term associations of SO_2 with BP and hypertension were investigated in six studies [23, 26, 29, 33, 36, 42], and five of them reported positive associations [23, 26, 29, 36, 42]. In a large population-based cohort from Germany (N = 2607), an increase in 5-day SO_2 by 75 $\mu g/m^3$ was associated with an increase in systolic BP by 1.07 mmHg (95% CI: 0.41, 1.73) [29]. Similar findings were reported in a population-based study in Taiwan (N = 9238): per increase in a 2-day lag SO_2 by 2 ppb, systolic BP increased by 0.32 mmHg (95% CI: 0.06, 0.59), and diastolic BP increased by 0.79 mmHg (95% CI: 0.61, 0.97) [42]. However, an inverse association with pulse pressure was reported in the latter study [42]. Similar to NO_2, SO_2 elevations were positively associated with hospital admissions for hypertension in two studies: per 10 $\mu g/m^3$ increase in daily SO_2 concentration, the estimated OR was 1.037 (95% CI: 1.004, 1.071) [26], and per increase in lag 3 SO_2 by 2.3 ppb, the estimated OR was 1.04; (95% CI: 1.00, 1.08) [36].

2.7. Other exposures

For the short-term exposure to CO, mostly null effects were reported with BP and hypertension as outcomes [29, 33, 36]. Inverse associations of short-term exposure to CO with systolic BP and pulse pressure, and null effects with diastolic BP were reported in one study [42]. Controlled exposure to diesel exhaust was associated with increased systolic but not diastolic BP in a study with 49 nonsmoking adults [21].

3. Long-term effects of air pollution

The number of studies on long-term effects of air pollution on BP is smaller, than the number of studies focusing on short-term effects, but has also increased tremendously in the last years. We identified 17 publications presenting individual studies investigating the long-term associations of air pollutants with arterial BP and hypertension [46–62]. Some of these studies have been included to the previous reviews [7, 12]. In addition to one cohort study, there has also been one metastudy, performed as a part of the European Study of Cohorts for Air Pollution Effects (ESCAPE; [63–65]). The ESCAPE study aimed to investigate the long-term effects of ambient air pollution on human health in Europe. More than 40 cohorts from 17 countries in Europe participated in the ESCAPE study [65]. Ambient air pollution concentrations in the participating cohorts were assessed according to the standard ESCAPE procedure [63]. The statistical analyses in ESCAPE contained two stages: (1) cohort-specific analyses using uniform statistical protocols and centrally developed analysis codes and (2) centrally conducted meta-analyses, followed by the publication of results in the peer-review articles.

Of the individual studies, seven were performed in North America (Canada and USA; [46, 56, 57, 59, 61, 62, 66, 67], five were performed in Southeast Asia (China and Taiwan; [47–51], and five studies were performed in Europe (Denmark, Germany, and Spain; [52, 53, 55, 58, 68]. The study samples in most studies included men and women [47–52, 54, 55, 58, 61, 66, 69]. Two cohorts included only women [56, 57, 59, 62], and one cohort included only men [46].

Most studies on long-term associations of air pollution with BP investigated systolic and diastolic BP as outcomes, and one study [59] investigated mean arterial pressure and additionally pulse pressure. The investigated exposures included $PM_{2.5}$, PM_{10}, soot, O_3, NO_x, and SO_2. All of the individual studies reported a statistically significant association with at least one of the BP parameters. However, only six studies observed concordant results with both systolic and diastolic BP [46, 48–50, 54, 58, 69]. In five studies, results varied across the BP metrics [47, 51, 52, 55, 59].

Nine studies investigated associations of air pollution with prevalent hypertension [47, 49–52, 55, 59, 63, 66, 67], five studies assessed only incident hypertension [56, 57, 61, 62, 64], and two studies analyzed both incident and prevalent hypertension [54, 58]. The majority of these studies reported positive associations of at least one pollutant with hypertension [49, 51, 55, 57, 61, 64, 66], indicating that air pollution is likely to have a prohypertensive effect. However, some studies observed negative [54, 57] or null [47, 52, 53, 58, 59, 63] associations.

3.1. Black carbon (soot)

Two markers of soot were used in the studies on long-term associations with BP and hypertension: BC [46] and absorbance $PM_{2.5}$ [47, 55, 63, 64]. Absorbance $PM_{2.5}$ is measured as the blackness of the $PM_{2.5}$ exposed filter in the particle sampler, determined by measurement of light reflectance. BC was positively associated both with systolic and diastolic BP [46]. The estimated associations with BP, adjusting for relevant confounders, were as follows: increase by 2.64 mmHg systolic (95% CI: 1.47–3.80) and 2.41 mmHg diastolic (1.77–3.05) per 0.32 $\mu g/m^3$ increase in black carbon [46]. Absorbance $PM_{2.5}$ was associated only with diastolic BP in single cohort analysis: 1) per increase by 10^{-5}/m, estimated increase in systolic BP was 0.15% (−0.49, 0.78) and in diastolic BP, 0.62% (0.24, 0.99); 2) per increase by 0.2 10^{-5}/m, the estimated mean change in systolic BP was 0.5% (95% CI: −0.1; 1.0), and in diastolic BP, 0.6% (95% CI: 0.1; 1.1; [55]). In the ESCAPE meta-analysis, where the association was assessed in medicated and nonmedicated participants separately, no association of long-term concentrations of absorbance $PM_{2.5}$ with BP was observed [63].

At 0.05 level of significance, none of the studies found an association with prevalence of hypertension. However, a weak positive relationship was observed in a German cohort: per increase by 0.2 10^{-5}/m in absorbance $PM_{2.5}$, percent change in hypertension prevalence was 10.8% (−1.1; 24.0; [55]). Incident self-reported hypertension (but not measured hypertension) was positively associated with absorbance $PM_{2.5}$ in the ESCAPE meta-analysis: per 10^{-5}/m increase in absorbance $PM_{2.5}$, the estimated RR was 1.13 (1.02, 1.24; [64]).

3.2. Coarse particles (PM_{10})

Three individual studies found positive associations of PM_{10} with both systolic and diastolic BP. An increase in PM_{10} per 48 $\mu g/m^3$ was associated with an increase in systolic BP by 16.34 mmHg (95% CI: 12.27, 20.42) and diastolic BP by 14.87 mmHg (95% CI: 12.73, 17.02) [48]. An increase in PM_{10} by 19 $\mu g/m^3$ was associated with an increase in systolic BP by 0.87 mmHg (95% CI: 0.48–1.27) and diastolic BP by 0.32 (95% CI: 0.08–0.56; [49]), and an increase per 3.9 $\mu g/m^3$ with an increase in systolic BP by 1.1 mmHg (95% CI: 0.2, 2.0) and diastolic BP by 0.8 mmHg (95% CI: 0.3, 1.2). In one study, PM_{10} was positively associated with

diastolic, but not systolic, BP [47]; in another study, systolic BP, pulse pressure, and mean arterial pressure were increased in association with PM_{10}, but not diastolic BP [59]. In the ESCAPE meta-analysis, no association of PM_{10} with BP was observed [63].

Two individual studies found positive associations of PM_{10} with hypertension, and per 10-μg/m^3 increase in PM_{10}, a hazard ratio (HR, a measure similar to the RR) for hypertension of 1.02 (95% CI: 1.00, 1.04) [67] was reported. In another study, per 20 μg/m^3 increase in PM_{10}, an increase in OR of 1.12 (95% CI: 1.08, 1.16; [49]) was reported. Two individual studies, on the contrary, reported no significant associations of PM_{10} with hypertension [47, 53, 58]. In the ESCAPE meta-analyses, no association of PM_{10} with incident or prevalent hypertension was observed [63].

3.3. Fine particles ($PM_{2.5}$)

So far, $PM_{2.5}$ is the most frequently investigated pollutant: 9 studies in total included it in the analyses with BP [47, 48, 50, 51, 55, 58, 63, 64, 69], and 10 studies included it in the analyses with hypertension [47, 50, 55, 56, 58, 61–64, 66, 67, 69].

Three individual studies reported a positive association of $PM_{2.5}$ with both systolic and diastolic BP [48, 50, 55, 58, 69]. Per increase in $PM_{2.5}$ by 20.42 μg/m^3, systolic BP increased by 32.08 mmHg (95% CI: 21.57, 42.58), and diastolic BP increased by 31.29 mmHg (95% CI: 25.43, 37.14) [48]. Another study has per 10 μg/m^3 increase in ambient $PM_{2.5}$ a 1.30 mmHg (95% CI: 0.04–3.56) increase in systolic BP and 1.04 mmHg (95% CI: 0.31–1.78) increase in diastolic BP [50]. The third study reported, per increase of $PM_{2.5}$ by 2.4 μg/m^3, an increase in systolic BP by 1.4 mmHg (95% CI: 0.5, 2.3) and an increase in diastolic BP by 0.9 mmHg (95% CI: 0.4, 1.4; [69]). Two studies reported a positive association with one of the BP parameters: per increase in $PM_{2.5}$ by 41.7 μg/m^3, an increase in systolic BP by 0.60 mmHg (95% CI: 0.05, 1.15; [51]), and per increase in $PM_{2.5}$ by 1 μg/m^3, an increase in diastolic BP by 0.7% (95% CI: 0.2; 1.2) [55]. No consistent associations were found in one individual study [47] and in the ESCAPE meta-analysis [69].

Six individual studies reported positive associations of $PM_{2.5}$ with hypertension: per increase in $PM_{2.5}$ by 10 μg/m^3, OR for hypertension of 1.05 (95% CI: 1.00–1.10) [66], HR for hypertension of 1.11 (95% CI: 1.03–1.19) [61], and OR for hypertension of 1.14 (95% CI: 1.07, 1.22) [50]. Per increase in $PM_{2.5}$ by 41.7 μg/m^3, OR of 1.11 (1.05,1.17; [51]), and per increase by 1 μg/m^3, an estimated OR of 1.145 (1.025; 1.280; [55]) were reported. Two individual studies reported no association of $PM_{2.5}$ with hypertension ([53, 56]). In the ESCAPE meta-analyses, no associations were observed for $PM_{2.5}$ with prevalent or incident measured hypertension [63, 64]. However, 5 μg/m^3 increase in $PM_{2.5}$ was associated with incident self-reported hypertension: RR of 1.22 (95% CI: 1.08, 1.37; [64]).

3.4. Ozone

Only two studies, both from the Asian region, investigated the association of long-term O_3 exposure with BP and both reported positive associations [48, 49]. The associations with BP were as follows: per increase in O_3 by 8.95 ppb, the estimated increase in systolic BP was 21.51 mmHg (95% CI: 16.90, 26.13) and in diastolic BP, was 20.56 mmHg (18.14–22.97; [48]), and per increase

in O_3 by 22 μg/m^3, systolic BP increased by 0.73 mmHg (95% CI: 0.35, 1.11), and diastolic BP increased by 0.37 mmHg (95% CI: 0.14, 0.61; [49]). Positive associations were also reported with hypertension: per increase in O_3 by 6.7 ppb, the estimated HR was 1.09 (95% CI: 1.00, 1.18; [57]) and per increase in O_3 by 22 μg/m^3, OR for hypertension was 1.13 (95% CI: 1.06, 1.20; [49]).

3.5. Nitrogen oxides

A 12.83 ppb increase in long-term concentration of NO_2 was associated with an increase in systolic BP by 14.40 (10.98–17.82) and diastolic BP by 12.43 (10.63–14.23; [48]). In a large cohort from Taiwan (N = 27,752), a positive association of nitrogen oxides with diastolic, but not systolic, BP was observed: per increase in NO_x by 20 μg/m^3, diastolic BP increased by 0.34 mmHg (95% CI: 0.19, 0.50) [47]. Another analysis with a Spanish cohort, vice versa, found association only with systolic BP: per 10 μg/m^3, increase in NO_2 systolic BP increased by 1.35 mmHg (95% CI: 0.23, 2.47). One study observed a positive association of long-term exposure to NO_2 with pulse pressure, but neither with systolic nor with diastolic BP [59]. No association of NO_2 with BP was found in two individual studies [49, 55] and also in the ESCAPE meta-analysis [63]. [52]. Contrary to the other studies, a negative association of NO_x with BP was observed in a large Danish cohort: per doubling of long-term NO_x, the estimated change in systolic BP was −0.50 (95% CI: −0.84, −0.16) and in diastolic BP was −0.24 (95% CI: −0.42, −0.07) [54].

NO_x was associated with incident hypertension in a longitudinal female cohort from the USA: per increase by 12.4 ppb, the estimated HR was 1.14 (95% CI: 1.03–1.25) [62]. However, in a later reanalysis with a larger sample, an inverse association was observed: per increase in NO_2 by 9.7 ppb, the estimated HR was 0.92 (95% CI: 0.86, 0.98) [57]. The authors do not consider the latter finding indicative of a causal relationship, but attribute it to the confounding relationship between NO_2 and neighborhood socioeconomic status in their study sample [57]. An inverse association of NO_x with prevalent hypertension was observed in the Danish study, similar to the findings with BP, but no clear associations with incident hypertension were reported [54]. At 0.05 level, no statistically significant associations were reported in six individual studies [47, 49, 52, 55, 59] and in the ESCAPE meta-analyses [63, 64].

3.6. Sulfur dioxide

The effects of SO_2 on BP and hypertension were investigated in two studies so far [48, 49]. One of these studies reported positive associations: per increase in SO_2 by 20 μg/m^3, systolic BP increased by 0.80 mmHg (95% CI: 0.46, 1.14), diastolic BP increased by 0.31 mmHg (95% CI: 0.10, 0.51), and OR for hypertension was 1.11 (95% CI: 1.04, 1.18; [49]). No association with BP was reported in the other study [48].

4. Effects in vulnerable subgroups

4.1. Children

Compared with adults and elderly, children are in the period of body growth and development. Therefore, children may be more susceptible to the effect of environmental pollution

exposure compared to adults. So far, six studies investigated the relationship between air pollution and blood pressure in children [43, 70–74], reporting mixed results.

Two of these studies investigated short-term effects of air pollution, reporting few positive associations [72, 74]. In a sample of 130 children aged 6–12 years, a positive association of daily ambient UFP exposure with systolic, but not diastolic, BP was observed: per increase in nano-sized UFP fraction by 860 particles/cm^3, systolic BP increased by 6.35 mmHg (95% CI: 1.56, 11.14) [72]. No associations with BP were observed for $PM_{2.5}$ and PM_{10} [72]. In a large Seven Northeastern Cities (SNEC) study from China (N = 9354, aged 5–17 years), PM_{10} and O_3, but not NO_2 and SO_2, were positively associated with hypertension, defined as ≥95th percentile of BP distribution by gender, age, and height [74]. An increase in 5-day mean PM_{10} by 47.4 μg/m^3 was associated with OR 2.17 (95% CI: 1.61, 2.93), and an increase in 5-day mean O_3 by 51.4 μg/m^3 was associated with OR 2.77 (95% CI: 1.94, 3.95) [74].

Four studies investigated long-term associations of air pollution with BP in children [43, 70, 71, 73]. In a cohort of German children (N = 2368, aged 10 years), long-term exposure to soot, $PM_{2.5}$, and PM_{10} was not associated with BP, and NO_2 showed a negative association, which diminished to null after adjustment for traffic noise [43]. In a cohort of Dutch children (N = 1147, aged 12–13 years), no consistent associations with short- and long-term exposure to PM and gaseous exposures were observed [70]. However, in a subgroup of children who have never changed their residence, a positive association of long-term exposure to NO_2 with diastolic BP was found [70]. A cross-sectional study (n = 179, aged 8–12 years) from Pakistan found systolic and diastolic BP in children living in areas with heavy traffic air pollution (mean daily value of $PM_{2.5}$: 183.0 μg/m^3) than in children living in areas with less traffic air pollution (mean daily value of $PM_{2.5}$: 28.5 μg/m^3) [73]. The most consistent positive signal was found in the analysis with the long-term exposure estimates in the SNEC study in China: 4-year mean PM_{10}, O_3, NO_2, and SO_2 were positively associated with BP and hypertension [71].

It is possible that short-term effect of air pollution on BP in children is stronger than long-term effect. The estimated short-term associations of exposure with hypertension in the SNEC study were stronger than the long-term associations [71, 75]. For example, the estimated ORs of PM_{10} with hypertension in boys, given per interquartile range, were 1.79–2.22 for short-term and 1.55 for long-term exposure [71, 75]. The same tendency was also observed with exposure to O_3 [71, 75].

There might be factors modifying individual susceptibility to adverse physiologic effects of air pollution in children. Stronger associations of air pollution with BP were observed in nonbreastfed children, compared to breastfed ones [71], in overweight/obese children, compared to those with normal weight [75], and in children with mood disorders or unfavorable emotional symptoms, compared to those with no emotional symptoms [76].

4.2. Pregnant women

Pregnant women usually are at particular risk for hypertensive complications since changes in pregnancy can lead to increased stress on the cardiovascular system [77]. Studies evaluating the relationship of ambient air pollution with BP and/or hypertensive disorders among pregnant women have been summarized in a recent review [12] and a systematic review and meta-analysis [77]. The meta-analysis revealed positive associations of multiple pollutants with

hypertensive disorders of pregnancy [77]. In particular, the following ORs were reported for combined pregnancy-induced hypertensive disorders: per 5 $\mu g/m^3$ of $PM_{2.5}$ 1.57 (95% CI: 1.26, 1.96), per 10 $\mu g/m^3$ of NO_2 1.20 (95% CI: 1.00. 1.44), and per 10 $\mu g/m^3$ of PM_{10} 1.13 (95% CI: 1.02, 1.26) [77]. The authors also found weak positive relationships with NO_x and O_3 [77]. No association with CO was found [77]. There is evidence of positive associations of air pollution with continuous BP levels in pregnancy, although the individual study findings differ by trimester [77].

5. Hypothesized pathophysiology

There are three potential pathways of how air pollution could affect BP: (1) triggering systemic inflammation and oxidative stress, (2) autonomous nervous system (ANS) imbalance, and (3) translocation of PM or its constituents into blood [7, 12]. It is suggested that pathways may, to some point, overlap in their action, although the exact interplay is unknown [12]. It is possible that a "vicious cycle" occurs, when reactive oxygen species (ROS) and pro-inflammatory cytokines, originating from the reaction of particles in the lungs or from particles penetrating into the blood flow, contribute to even more oxidative stress and damage to the vascular system.

Inhalation of air pollutants could trigger an inflammatory response in the alveoli [12]. The inflammatory response is reflected in generation and release of the endogenous pro-inflammatory mediators, such as cytokines (interleukins 1 and 6 (IL-1, IL-6), tumor necrosis factor, acute phase response molecules (c-reactive protein and fibrinogen), activated white blood cells, platelets, and vascular-active molecules such as endothelin in the lung. Further, these mediators could reach the systemic circulation, potentiating the systemic inflammatory response and oxidative stress. This results in excessive generation of ROS and reactive nitrogen species (RNS). Under normal conditions, these substances help maintain vascular integrity [78]. However, the abundance of ROS and RNS can harm the vessels, triggering endothelial dysfunction, smooth muscle cell apoptosis, and inflammatory and other damage to vessels [79].

According to the second proposed mechanism, the sympathetic branch of ANS, which directs the "fight and flight" response, gets activated, while the parasympathetic ANS, leading the group of so-called rest and digest reactions, gets inhibited [12]. It is likely that inhaled particles trigger autonomic imbalance through activation of afferent pulmonary autonomic reflexes [12]. In a controlled human exposure study, acute imbalance of autonomic nervous system, which is characterized in the activation of sympathetic nervous system and withdrawal of parasympathetic nervous system, was the most likely underlying mechanism of the rapid increase in diastolic BP following particle inhalation [80]. The autonomic imbalance, resulting from the short-term exposure to elevated levels of air pollutants, is characterized by reduced heart rate variability and a rapid increase in BP [12]. Apart from the acute response, it is possible that autonomic imbalance is involved in chronic adverse cardiovascular effects of air

pollution, since there are some indications that sympathetic ANS is involved in long-term regulation of BP [81].

The third hypothesized mechanism suggests that nanoparticles and soluble compounds (e.g., metals) of the air pollution mixture can translocate to the systemic circulation [4]. In addition to translocation by diffusion, the particles could be ingested by alveolar macrophages [4]. The particles or their soluble components, having entered the circulation, can interact with the vascular endothelium or induce local inflammatory response and oxidative stress, similar to the response in the lung [4].

The core pathophysiologic process underlying cardiovascular effects of air pollution is oxidative stress, an imbalance between the production of ROS and RNS, and their neutralization through antioxidant defense [7]. Oxidative stress is a generic mechanism of injury involved in many pathologic processes and plays a very important role in the pathogenesis of cardiovascular disease [82]. Elevated levels of ROS, reduced bioavailability of NO, and inhibited antioxidants in blood have been observed in animal and human studies of hypertension [78, 82]. Though it has not been proved that oxidative stress may cause hypertension, it can augment the existing prehypertensive condition [78]. The elevated levels of ROS can lead to adverse processes such as endothelial dysfunction, increased contraction, vascular inflammation, and vascular remodeling [78]. Oxidative stress can lead to cell proliferation, hypertrophy, and collagen deposition in vascular wall; can stimulate the expression of pro-inflammatory molecules, such as adhesion molecules and chemotactic proteins; and can mediate the oxidation of lipids and cell migration [79]. In the outer vascular layer, ROS can lead to vascular remodeling [78]. Vascular remodeling, which is considered to have a causal relationship with hypertension, is a combination of pathological changes of small arteries characterized by a reduced lumen and increased media-to-lumen ratio [83]. Oxidative stress within the renal medulla can also promote renal dysfunction and contribute to elevated BP [78, 82]. Oxidative stress in the central nervous system could, through the activation of the sympathetic ANS, also contribute to hypertension development [82].

Vascular endothelium maintains vascular homeostasis through the interactions with the cells in the vessel wall [84]. Endothelial dysfunction is a combination of impaired vasomotion and vascular tone, the prothrombotic and pro-inflammatory changes, and proliferation in the arterial wall, characterized by the inability of the endothelium to dilate in response to vasodilator stimuli [82, 84]. Inflammation and oxidative stress can potentiate the development of endothelial dysfunction. For example, vascular oxidative stress can result in decreased bioavailability of NO [79]. Combined with an inflammatory response, this may promote endothelial dysfunction [79]. Oxidative stress and endothelial dysfunction are prevalent in subjects with hypertension and therefore have been suggested to play causal roles in hypertension development [85]. It is possible that the prohypertensive response to long-term exposure is potentiated through endothelial dysfunction, as a delayed (24 hours postexposure) endothelial dysfunction was observed in the controlled air pollution exposure study with healthy volunteers [80]. Authors hypothesized that this response was triggered by inflammatory reactions [80].

6. Related environmental exposures

6.1. Interaction of noise and air pollution on hypertension

Alongside air pollution, ambient noise is a major environmental risk factor in the urbanized societies. Noise is a stressor that can affect the endocrine and sympathetic ANS and trigger unspecific physiological responses, such as elevated BP, heart rate, vasoconstriction, release of stress hormones, and so on [86]. Such responses favor development and progression of cardiovascular disease, such as hypertension. Two systematic meta-analyses showed positive statistically significant associations of road traffic and aircraft noise with hypertension: per 5 dB of traffic noise, OR of 1.034 (95% CI: 1.011, 1.056) [87], and per 10 dB of aircraft noise, OR of 1.13 (95% CI: 1.00, 1.28) [88]. The evidence for railway noise is rather limited, but positive associations with residential exposure to railroad noise were reported in a population-based Swiss study [89]. Noise annoyance was also positively associated with hypertension in a systematic meta-analysis [90].

Long-term ambient noise exposure shares many sources with outdoor air pollution. Therefore, if not properly controlled for, it may confound air pollution estimates in the analyses. A systematic review was conducted to assess whether the associations of traffic noise or traffic-related air pollution with cardiovascular outcomes could be mutually confounded [91]. The authors concluded that traffic-related air pollution and noise do not mutually confound each other in most of the reviewed studies [91]. The effects of air pollution and noise are likely independent, and there is no interaction between them, or such interaction is probably very small [91]. Indeed, few studies appear to suggest that traffic noise and air pollution may independently contribute to the risk of hypertension [53, 55, 63, 64]. However, more research is recommended to estimate the extent of potential confounding factors [91, 92].

6.2. Ambient temperature, climate change, and BP

It is well known that ambient temperature can affect BP [93]. A recent random-effects meta-analysis, which included 14 studies, indicated that a decrease of 1°C in mean daily outdoor temperature was associated with an increase in SBP and DBP of 0.26 mmHg (95% CI: 0.18–0.33) and 0.13 mmHg (95% CI: 0.11–0.16), respectively [94]. A stronger response was observed in subgroups of subjects with CVD conditions [94].

Ambient air pollution and temperature show synergistic effects on BP. A recent panel study with healthy volunteers found that the association of air pollution with BP was stronger at lower temperatures and, vice versa, the effect of outdoor temperature on BP was only found at high air pollution levels [95]. Also, the effects of individual pollutants may vary by season: in a large cohort study, the associations of PM_{10} and NO_2 with BP were found in the warm season, while SO_2 and O_3 were associated with BP in the cold season [96].

Climate change might contribute to the association of air pollution with BP and hypertension beyond the temperature effects. For example, the concentration of tropospheric O_3 is expected to increase due to global climate change [97]. O_3 was linked to various CVD events, such as

ventricular arrhythmias, myocardial infarction, and ischemic heart disease in the recent studies [97]. Soil drying, deforestation, drought- and climate change-induced dust storms, and wildfires reduce air quality and can increase the concentration of PM dramatically, therefore escalating respiratory and CVD disease burden [97]. It is expected that concentrations of $PM_{2.5}$ from anthropogenic sources will increase with climate change, as, in addition to emissions, there will be changes in meteorology and in physical and chemical transformations of particles in the atmosphere [98].

7. Conclusions

The number of studies on short-term effects of air pollution in the general population has grown in the recent years. Based on the reviewed evidence, we can conclude that an acute increase in air pollution was associated with a transient increase in arterial BP within the following hours or days. Moreover, short-term elevations in air pollution were associated with hospital admissions for hypertension, even at relatively low exposure levels. Most studies focused on PM exposure. Despite some heterogeneity in results, the evidence is in favor of acute increase in BP and hypertension episodes following exposure to fine and coarse PM.

The evidence of short-term effects of gaseous pollutants is still rather scarce and more heterogeneous. Most consistent findings are observed in studies with NO_2 and SO_2, reporting short-term associations with BP and emergency visits for hypertension. There are fewer studies with less consistent results with O_3 and CO, as well as for other types of air pollutants, calling for more research in this field.

As for long-term effects of air pollution, the evidence is somewhat more limited, than for the short-term effects. However, the number of studies is increasing over years, allowing comprehensive comparisons of the effect estimates for different types of air pollutants. Similar to the studies on short-term effects, most cohort studies on long-term effect report positive associations of at least one pollutant with systolic and/or diastolic BP. The majority of studies also report some positive associations of hypertension, though there are more null findings, than with BP. The vast majority of publications on long-term air pollution with BP focused on PM as exposure, similar to the studies on short-term effects. The most consistent positive associations with BP and hypertension were reported for fine particles (PM_{10} and $PM_{2.5}$). Only few studies investigated the associations with gaseous pollutants. Results with NO_x were rather mixed. There are few studies investigating O_3 and SO_2, reporting some positive associations. More longitudinal studies, assessing a simultaneous effect of (1) short- and long-term exposures and (2) various pollutants separately and combined is needed for complete understanding of the effect size, relevant time window of exposure, and the responsible pollutants.

These findings are similar to the previous reviews [7, 12]. However, we expanded the previous reviews by focusing on studies in the general population and by a detailed investigation of the evidence by the type of pollutant, duration of exposure, and type of BP-related outcome studies.

There is accumulating evidence on positive association of air pollution with BP in children. Childhood growth and development of cardiovascular system might be the age of special vulnerability of the cardiovascular system toward the environmental influences. It is also possible that short-term effects of air pollution are stronger in children than in adults. Pregnant women may be another specifically vulnerable population group in regard to prohypertensive effect of air pollution.

Plausible biologic pathways, involving inflammation, oxidative stress, sympathetic ANS activation, endothelial dysfunction, vasoconstriction, and small artery remodeling, are proposed to explain how air pollution could affect blood pressure. Longitudinal epidemiologic studies with extensive clinical examinations, repeated over years, could provide more information for better understanding on the sequence of events in the air pollution–related cardiovascular disease development or progression.

It is important to consider air pollution together with other environmental risk factors. For example, ambient noise shares many common causes with air pollution. It is possible that the associations of air pollution and noise with BP are independent and not confounded by each other. However, some studies do not confirm this, and it is advisable to account for potential confounding factors by adjusting for ambient noise when investigating the cardiovascular effects of air pollution. Another important environmental factor is climate change. It can affect human health independently of air pollution, but it can also influence the composition and toxicity of air pollution mixture. It is possible that climate factors and air pollution act synergistically on BP and hypertension.

Conflict of interest

The authors declare no conflict of interests.

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Chapter 3

Hemodynamic Considerations in the Pathophysiology of Peripheral Neuropathy

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Additional information is available at the end of the chapter

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Abstract

Peripheral neuropathic pain presents one of the greatest on going challenges to both acute and chronic pain management yet our understanding of the origins and pathogenesis of this complex disease state are severely lacking. The purpose of this chapter is to review the current literature regarding neuropathic pain as impacted by hemodynamic alterations. Because of the varied origins of neuropathy, this cannot be discussed as a single entity but we can seek to identify a final common pathway. We will for this reason examine each known pathogenetic category of neuropathy separately then discuss the effect of hemodynamic alterations through changes in blood pressure to determine any correlations between these alterations and specific effects upon neural structure and function. We have divided this chapter into sections which describe the more commonly known and encountered neuropathies. These are diabetes mellitus, neurotoxic medications, alcohol-related neuropathy, Vitamin B_{12} deficiency, end-stage renal disease, inflammatory bowel disease, and rheumatoid arthritis.

Keywords: peripheral neuropathy, pathophysiology, classifications, mechanisms, molecular basis, incidence, literature review

1. Introduction

Peripheral neuropathy is a relatively rare but well-known degenerative disorder of the peripheral nervous system with an estimated overall annual incidence of 1.6 per 100,000 and a prevalence of 2.4% in the United States [1, 2]. For persons forty years and older, the prevalence is about five-fold higher (11.5%) and 10 times higher in diabetic individuals (21.2%) [3]. Among the causes of peripheral neuropathies are caused by diabetes mellitus, toxins, alcohol abuse, or paraneoplastic syndromes. The most common cause of peripheral neuropathy worldwide is

diabetes mellitus. Both sensory and/or motor component (sensorimotor) of the peripheral nervous system can be affected. The symptoms, severity and duration of peripheral neuropathy depend on the type of nerve affected, sensory, motor or both, the inciting incidence or causative agent, and the length of exposure. Motor neuropathy is characterized by muscular weakness affecting mobility, coordination, and respiratory function. Sensory neuropathy is characterized by pain, numbness, burning sensation, absent or diminished reflexes and sensation to touch.

2. Background

2.1. Vascular supply to peripheral nerves

The vascular supply to peripheral nerves is often overlooked both in the natural history of common, well-understood diseases as well as in the management of acute and chronic pain syndromes. When chronic peripheral neuropathic pain develops the results can be devastating with significant impairment in quality of (QoL) functioning in the activities of daily living (ADL) and cause significant loss of income as well as lost productivity in the workplace. This chapter will focus primarily upon the vasa nervorum which are the vessels that supply the peripheral nerves. The chapter will review, first, the embryology of the vasa nervorum, then the resultant anatomy and the physiology of these vessels. This section will provide the groundwork for the discussion of molecular pathways that cause changes to both the integrity of these vessels as well as the diminution in the number of functional vessels.

2.2. Summary of neural lesions

Emphasis will be placed upon the second crush theory as a mechanism of vasculopathic contribution to decreases in axonal transport mechanisms (**Figure 1**), as well as specific diseases and drug interactions that result in perfusion dependent mechanisms of neural injury (**Table 1**). These syndromes will include diabetic neuropathy, rheumatoid arthritis-associated neuropathy; Vitamin B_{12} deficiency- neuropathy; hypertensive and hypotensive neuropathy; chemotherapy and radiation neuropathies.

2.3. Neuropathies and double crush

It should be noted that peripheral neural blood flow has been thought to present as a double edged sword in the development of certain neuropathies. In a 1994 study, Jaap et al. examined the maximal microvascular hyperemic response to local heating in subjects with fasting hyperglycemia and compared these to healthy, age and sex matched controls [4]. Bandla et al. in at least one setting speculated that diminished flow may be beneficial. In this work they examined 15 healthy human subjects and explored the use of continuous flow, limb hypothermia to limit the delivery of chemotherapeutic agents to peripheral nerves. No further studies have been reported with this specific model yet it serves to broach the theory that reduced delivery of toxins may be protective [5]. And In another suggestive study, perfusion effects in patients with established neuropathic pain were examined and compared to healthy controls using dynamic contrast-enhanced magnetic resonance imaging. Time-signal intensity

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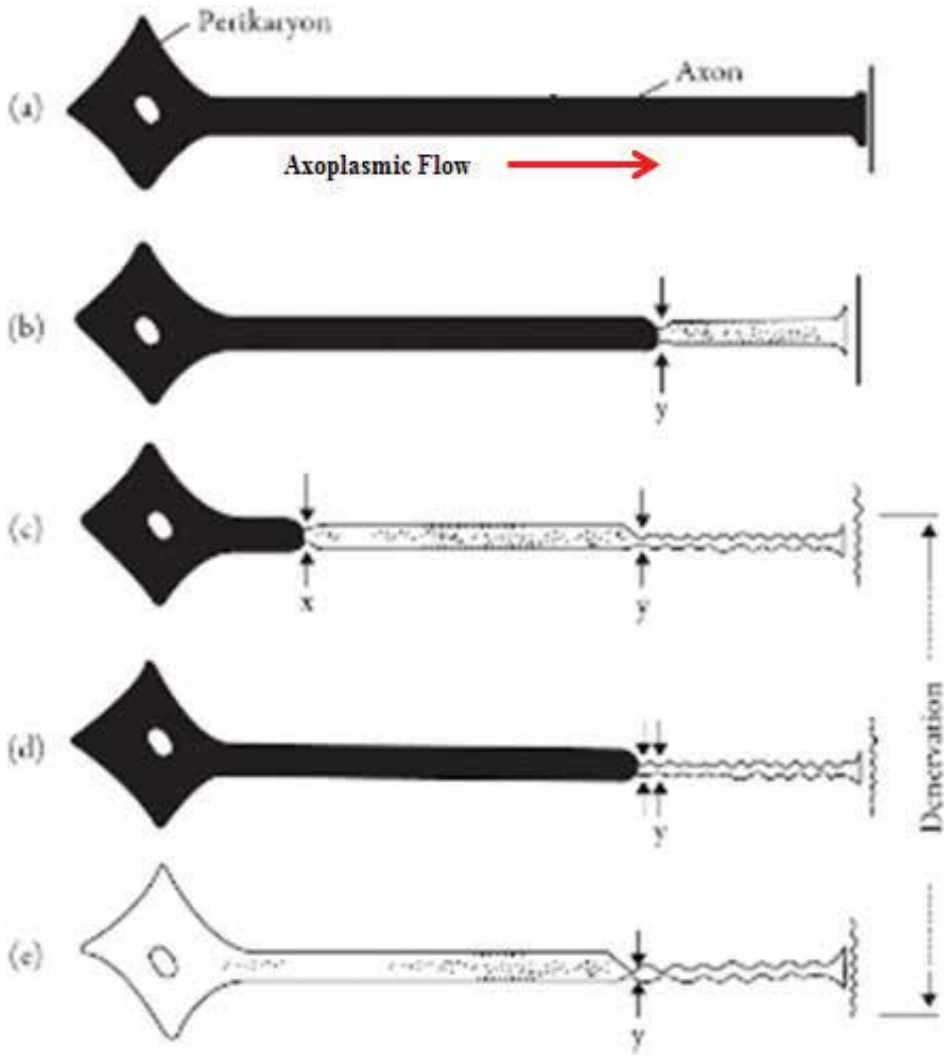

Figure 1. Different types of neural lesions that can lead to denervation. Axoplasmic material is represented by the density of the shading. Completely healthy neuron (a) axoplasmic flow is complete. (b) In a healthy neuron with one area of mild compression flow is maintained distal to a compressive point indicated by "y". (c) In a healthy neuron with two mild compressions, disruption of flow and thus denervation occurs distal to "y" which is the point of compression. (d) Denervation.

analysis showed significantly increased contrast uptake in patients with neuropathy and was determined to be the result of increased blood-nerve permeability [6].

Finally the chapter will focus upon interventions that may allow for not only treatment of these neuropathies at the earliest stages of their presentations but also preventive measures in patients at risk.

It is our hope that this chapter will not only elucidate these mechanisms of disease but also stimulate discussions which will lead to further research into this component of neuropathic disease in the hope that better patient treatment options may be developed.

Neuropathies Associated with Increased Risk of Second Crush Injury

Neuropathy	Vasa Nervorum Mechanism	Perfusion Dependent	Axonal Transport Defect	Baseline Flow Characteristics of Neural Environment (Goals)
Diabetes	Microvascular cell loss occurs, progressive capillary occlusion	Yes	Yes	Maintain
Rheumatoid Arthritis	Reduction in number of vessels of vascular supply of nerves due to endothelial apoptosis	Yes	Yes	Maintain
Inflammatory Bowel Disease	Microvascular ischemic demyelination	No	Yes	Maintain
Vitamin B_{12} Deficiency	Not known	No	Yes	Maintain
Alcoholic	Not known	Unclear	Yes	Maintain
Hypertension/ Hypotension	Diminished flow	Yes	Yes	Maintain
Uremia	Degradation of Na^+/K^+ Pumps Disrupts Neuronal Integrity	Unclear	Yes	Maintain
Platinum	↓ in vascular endothelial cells	Yes	Yes	Maintain

Table 1. Neuropathies associated with risk of double crush injury.

3. Causes of peripheral neuropathy

3.1. Diabetic neuropathy

Diabetic Peripheral Neuropathy is a common neurological manifestation of both type I and type II diabetes, affecting up to 50% of diabetics with an even greater incidence in those with subclinical manifestations. The peripheral neuropathy can involve both motor and sensory

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nerves and the complexity of the metabolic and vascular factors involved has still not been fully elucidated. The sensory loss is classically described as a "stocking and glove distribution" involving both hand and legs. The underlying pathology causing this neuropathy appears to involve both macro and microvascular processes.

3.1.1. Galactose neuropathy

As far back as 1984 galactose was implicated as a cause for peripheral neuropathy in a murine, diabetic model. Using C14 iodoantipyrine as a radioactive tracer of tissue perfusion, the group noted a significant decline in nerve blood flow in animals that had ingested galactose for 6 months vs. controls. There was also a positive correlation between galactose ingestion, endoneurial edema, increased tissue pressure, and ultimate demyelination of nerve fibers. The group also found that Schwann cells showed significant glycogen accumulation in regions in which there was edema. This bolstered the argument that edema, rather than neural hyperactivity in the sorbitol pathway was responsible for the pathological changes in galactosemic neuropathy [7].

3.1.2. Diabetes and autonomic function

Another study examined peroneal nerve conduction velocity as a primary outcome of neural function and correlated this to the severity of diabetic neuropathy. Mallamaci et al. studied autonomic function in uremic patients and were able to show a weak non-statistical relationship between an improvement in neurologic function and post-renal transplant status [8].

Dillon et al. concluded that slow-healing of neuropathic ulcers was associated with a loss of cholinergic nerve function, that cholinergic stimulation will increase capillary blood flow and indirectly suggested that improved blood flow to the neural supply of the region may have an overall beneficial effect to the insulted tissue [9]. In 1997 the same group advanced their work to conclude that peripheral blood flow is inversely related to the degree of peripheral neuropathy [10].

3.1.3. Obstructive sleep apnea and oxidative stress

The role of oxidative stress in the pathogenesis of diabetic peripheral neuropathy as it was related to obstructive sleep apnea was studied. There was a 65% incidence of OSA in diabetic patient with DPN. In patients with diabetes and OSA, there was a prevalence of 60% of diabetic peripheral neuropathy. However, in diabetic patients without OSA, the prevalence was 27% of diabetic peripheral neuropathy ($p < 0.001$) [11]. A theory for the precise mechanism of this correlation was not discussed.

3.1.4. Role of angiotensin

Angiotensin-converting enzyme was considered as early as 1998 as playing a role in the treatment of human diabetic neuropathy in a randomized trial. In this work 41 patients with normotension, "mild" diabetic neuropathy and a diagnosis of type I or type II diabetes were placed in the randomized double-blind placebo-controlled trial. Assessments of treatment efficacy were made using the endpoint of neuropathic symptoms, deficit scores, vibratory perception threshold, peripheral-nerve electrophysiology, and cardiovascular autonomic function at 6 and 12 months of treatment with the primary endpoint of change in peroneal

motor nerve conduction velocity. The study revealed a significant increase in peroneal motor nerve conduction velocity, M-wave amplitude and sural nerve action potential amplitude (p = 0.03). However vibration-perception threshold, autonomic function and the symptoms of neuropathy and deficit score showed no improvement in either group. Yet the question remains whether neural functional impairment can ultimately lead to symptomatic improvement and further clinical study is needed to make this determination [12].

3.1.5. Glycochelates and transition metals

The role of transition metals was argued in a review article by Qian et al. in 2000. They presented data that heavily glycated proteins known to accumulate in individuals suffering from diabetes gain an increased affinity for transition metals such as iron and copper. This affinity results in the accumulation of bound metal by elastin and collagen within the arterial wall. The bound metal is believed to cause the catalytic destruction of endothelium-derived releasing factor (nitric oxide or a nitric oxide derivative). The loss of vasodilatory ability (or chronic vasoconstriction) impairs blood to peripheral nerves with resultant deprivation of oxygen and critical nutrients. The authors cite initial studies that suggest the administration of chelators such as desferrioxamine may prevent or reverse slower peripheral nerve conduction and neuronal blood flow [13].

3.1.6. Endothelial control of microcirculation

The role of endothelium-dependent and endothelium-independent microvasodilation and their relationships to neural microcirculatory control was examined in type I and type II diabetic patients by Kilo et al., in 2000. They used iontophoresed acetylcholine and nitroprusside studied in a dose–response technique to elicit C-fiber mediated vasodilation. As expected, endothelium-dependent vasodilation of the cutaneous microcirculation was attenuated in type II diabetic subjects vs. control; however there was no significant difference between the endothelium-dependent vasodilation in type I diabetics vs. controls. There was no difference between either diabetic group (type I or type II) regarding endothelium-independent vasodilation. They also found that the C-fiber- mediated axon reflex was impaired in both type I and type II diabetics, which the group stated was consistent with a small fiber neuropathy. The study led to the conclusion that endothelial function and nitric oxide play a significant role in the pathogenesis of peripheral neuropathy in type II diabetic patients and that this disease process is the result in part of significant C-fiber impairment. Again, the function of C-fibers, the neural component of peri-neural hemodynamics, and the peri-neural chemical milieu may begin to suggest a common pathway for the perfusion of peripheral nerves and the development of peripheral neuropathy [14].

3.1.7. Axon reflex vasodilation

Axon reflex vasodilation was induced by histamine iontophoresis to assess cutaneous afferent C-fiber function in a diabetic human model. In 2000, Schuller et al. used this approach to measure cutaneous vasoconstrictor responses. The group also used two other neurophysiological methods to assess small nerve fiber function in patients with non-diabetic peripheral neuropathy: heart rate variation tests to assess cardiac parasympathetic small fiber function,

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and cutaneous vasoconstrictor response (sympathetic C fibers) induced by deep inspiration measured by laser Doppler flowmetry. Based on the study results the authors implied that functionally different systems (parasympathetic, sympathetic, and sudomotor) may be affected separately and can and should be tested separately. This consideration may be of use in constructing experimental human models to test various neuropathy treatment interventions [15].

3.1.8. Genetic therapy of diabetic neuropathy

Reversal of experimental diabetic neuropathy in a murine model induced by two different techniques was explored by Schratzberger et al. in 2001. Both streptozotocin- and alloxan-induced diabetes models were employed and nerve blood flow was assessed by laser Doppler imaging or direct detection of a locally administered fluorescent lectin. In both models intramuscular gene transfer of plasmid DNA encoding VEGF-1 or VEGF-2 resulted in increases in vascularity and nerve blood flow to levels found in control animals. The group also reported that constitutive over expression of both transgenes resulted in restoration of large and small fiber peripheral nerve function as measured by motor and sensory nerve conduction velocities. Similar findings in a lapine model are also reported. There is accumulating evidence, then, that genetic therapy may have a role in the treatment of peripheral neuropathy of diabetic origin. Unlike the observed efficacy of this gene therapy in chemotherapy-induced neuropathy considerations for induction of related angiogenesis would not be a factor in the decision to institute plasmid DNA therapy; however a concern for possible retinal angiogenesis and a question of initiating or worsening diabetic retinopathy may be a concern. In this regard further research is needed first to assess the associated angiogenicity of this treatment in animals and second to establish whether any benefit of the therapy can be extrapolated to a human model [16].

3.1.9. Protein kinase

Protein kinase inhibition was examined in a work by Casselini. In this study they reported that over-activation of the enzyme and microvascular dysfunction resulted in the disordered skin changes observed in diabetic peripheral neuropathy. Their study concluded that in patients with DPN ruboxistaurin-enhanced skin blood flow at the distal calf reduced sensory symptoms and improved quality of life (QoL) as measured by the Norfolk QoL-DN [17].

The role of inhibition of protein kinase C (PKC) in the study of experimental diabetes in a human model was discussed by Sasase et al. 2006. Specifically they emphasize the effects of hyperglycemia-induced PKC activation and the subsequent altered hemodynamics, angiogenesis, vasoconstriction, endothelial permeability, cell growth, cytokine activation and leukocyte adhesion. Their discussion asserts that PKCβ inhibitors were well-tolerated in clinical trials and that this inhibition may therefore represent a promising approach to the treatment of diabetic complications [18].

3.1.10. Nitrosative stress

The nitrosative stress argument was further discussed in a 2007 paper by Obrosova et al. In this work they found that streptozotocin-induced diabetic rats that were maintained with the

peroxynitrite decomposition catalyst FP15 exhibited a dose-dependently corrected improvement in the neuropathic disorders that occurred secondary to experimental diabetes. These disorders were sensory and motor nerve deficits; mechanical hyperalgesia, and tactile allodynia in the absence of small sensory nerve fiber degeneration. FP15 was also found to correct endoneurial nutritive blood flow and nitrotyrosine fluorescence in aorta and epineurial arterioles, indicating that it helped maintain vessel integrity. In addition FP15 alleviated diabetes-induced decreases in acetylcholine-mediated relaxation of coronary and mesenteric arteries. The findings iterate the significance of nitrosative stress in the development of neuropathy as well as vasculopathy and suggest that further studies of PDCs in the treatment of experimental diabetes are needed [19].

The role of peroxynitrite-mediated nitrosative stress in the development of diabetic neuropathy was studied in a murine model by Negi et al. in 2010 [20]. In this work the effect of a combination of peroxynitrite decomposition catalyst (PDC), FeTMPyP [21], and a poly (ADP-ribose) polymerase (PARP) – a nuclear enzyme activated after detection of DNA damage-inhibitor [22]. The rationale for the use of the PARP inhibitor was the role that overactivation of this enzyme is believed to play in the development of diabetic neuropathy [23]. The group studied the following endpoints: motor conduction velocity and nerve blood flow for evaluating neural function; malondialdehyde and peroxynitrite levels to detect oxidative stress-nitrosative stress; and NAD concentration in sciatic nerve to assess NAD overproduction of PARP. Treatment with combination of FeTMPyP and 4-ANI led to improvement in neural function and also attenuated the oxidative-nitrosative stress markers. The combination also reduced the overactivation of PARP which was demonstrated by increased levels of NAD and by the demonstration of decreased PAR immunopositivity in sciatic nerve microsections. The authors concluded that treatment with a combination of a PDC and a PARP inhibitor attenuates alterations in peripheral nerves in experimental diabetic neuropathy.

3.1.11. Resistin

Serum levels of the adipokine resistin were shown to correlate with systolic blood pressure, diastolic blood pressure and epithelium (ET); and to negatively correlate with nitric oxide. More recently [25] resistin was shown to actively induce hypertension and insulin resistance in wild type mice believed to occur by the upregulation of angiotensin (Agt) toll-like receptor 4 expression. In toll-like receptor 4 (tlr4) negative mice or in mice treated with the angiotensin-converting enzyme inhibitor, perindopril resistin had no effect. The authors concluded from this that resistin activates the renin- NF angiotensin system via the TLR4/P65-NFKB subunit/Agt pathway which links insulin resistance to hypertension. The higher serum resistin levels in patients with diabetic neuropathy vs. diabetics without peripheral neuropathy suggests that resistin may play a role in the pathogenesis of type II diabetes and diabetic peripheral neuropathy. The question is also raised regarding whether hypertension secondary to resistin is a causative factor in this neuropathy (**Figure 2**) [24, 25].

3.1.12. Endothelial dysfunction

The relationship between endothelial and neutral control of skin blood flow (SkBF) in patients with diabetic peripheral neuropathy was studied by Brooks et al. in 2008 [27]. It is worth noting here that in this study, which examined the effect of the isoform protein kinase C

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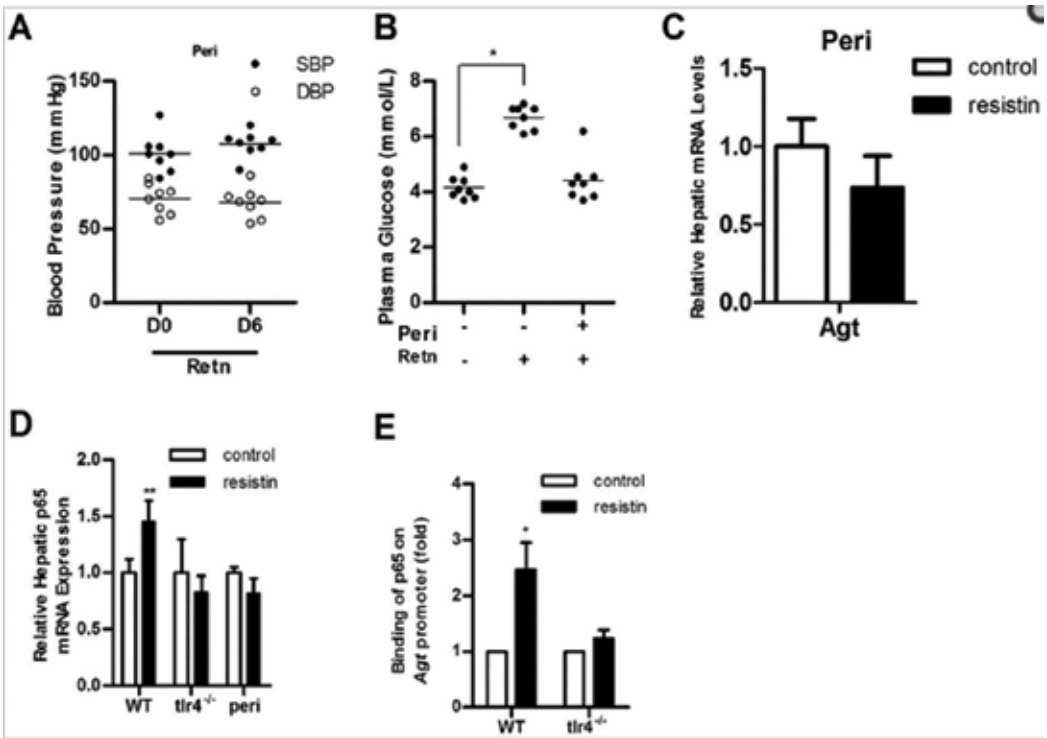

Figure 2. Perindopril blocks the action of resistin. (A) BP in wild-type mice pre-treated with perindopril (Peri). BP was measured before resistin treatment (day 0, D0) and after 6 days of resistin treatment (day 6, D6); (B) plasma glucose levels in mice exposed to different treatments; (C) Agt and (D) p65 expression in mice exposed to different treatments and in different mouse lines; (E) binding of p65 to the Agt promoter was determined by chromatin immunoprecipitation. The resistin group (Retn) was injected with 400 ng/day resistin; while the control group was injected with PBS (control-vehicle). Perindopril (5 mg/kg/day) was administered orally for 7 days (animals were treated as described in Materials and Methods). Data are presented as mean ± SD ($n = 8$). $^{*}p < 0.05$, $^{**}p < 0.01$ (adapted from Jiang et al.. [25]).

inhibitor ruboxistaurin (which has been shown to slow or reverse the progression of diabetic neuropathy) [26]; the group found that while RBX had no direct effect of skin blood flow they did find correlation between C-fiber mediated and endothelium-dependent skin blood flow at baseline. The importance of this finding was that it suggested that improving endothelial function could positively affect microcirculation via the neurovascular arcade [27]. Zakareia et al. in 2008 concluded that the rise in vascular endothelial growth factor (VEGF) in diabetic neuropathy may be protective and preserve neural blood flow, and that the significant rise in soluble fatty acids may be causative in the advancement of neuropathy [28].

Pek et al. in 2015 further studied the relationship between endothelial dysfunction and arterial stiffness and diabetic neuropathy [29]. This group collected data on blood chemistry, arterial stiffness by carotid-femoral pulse wave velocity (PWV) and endothelial function by laser Doppler flowmetry. The group recruited 2054 patients 2014 of whom met the criteria for a diagnosis of diabetic peripheral neuropathy (DPN). The presence of DPN in this work was defined as either impaired light touch sensation tested using the 10 g monofilament (<7/10 on either foot) or a neurothesiometer (which compares vibration perception thresholds) (Young, 1993) reading of ≥25 V. Patients with DPN were significantly older (60.1 ± 9.9 vs.

57 ± 10.8 years); had a longer duration of diabetes (15.8 ± 10.0 vs. 10.9 ± 8.6 years); had a higher systolic blood pressure (146 ± 20.6 vs. 137.6 ± 18.7 mmHg); and a higher pulse wave velocity (11.5 ± 3.5 vs. 9.5 ± 2.7 m/s); poorer endothelium-dependent vasodilation (73.4 (33.9–141.3) vs. 105.7 (51.2–175)%); and poorer endothelium-independent vasodilation (54.6 (31.2–80.6) vs. 68.3 (38.2–108.2)%).

These findings contribute to the argument that hypertension and poor vascular compliance are risk factors for peripheral neuropathy in clinical diabetes. It should be noted that it may prove an ever more daunting task to extrapolate findings from non-human, experimental diabetic neuropathy models to the human disease process.

3.1.13. Sodium-hydrogen exchanger

In 2013, Lupaychyk et al. examined the neuropathic endpoints of motor and sensory nerve conduction velocities in sciatic motor and sensory nerves, endoneurial nutritive blood flow, vascular reactivity of epineurial arterioles, thermal nociception tactile allodynia and intraepidermal nerve fiber density in a streptozotocin-diabetic murine model following administration of cariporide. The Na^+/H^+ exchanger-1 inhibitor partially reversed the diabetes induced motor and sensory nerve conducting deficits; thermal hyperalgesia; tactile allodynia and intraepidermal nerve fiber loss. Cariporide was also associated with reduction of diabetes-induced accumulation of advanced glycation end-product, oxidative stress and nitrated proteins in the sciatic nerve. The study did not proffer a mechanism for the action of the drug in this role; however NHE activation has been known to result in calcium overload in some cell types while inhibition of NHE appears to prevent reperfusion injury. Of particular interest with the use of this class of drugs, is their potent scavenging capacity of oxidizing free radicals which can proceed to damage many cellular components including phospholipid A- containing cellular membranes [30–32].

3.1.14. Puerarin

The effect of the isoflavone, Puerarin, was assessed in a review by Wu et al. in 2014. The evaluation of relatively low quality studies involving 1664 via meta-analysis showed that Puerarin injection combined with western medications was more effective than conventional therapy for diabetic peripheral neuropathy in terms of nerve conduction velocity and hemorheologic index. Although suggested by the review: it is not specifically indicated that pressure dependent neurovascular blood flow correlates with symptomatic improvement through use of this vasodilator [33].

3.2. Rheumatoid disease

The existence of neuropathic pain in rheumatic disease has been described in the literature. Most of these discussions have involved rheumatoid arthritis, systematic lupus erythematosus and systemic vasculitis, and the incidences of neuropathic pain in these populations have been limited. In variants of rheumatoid disease with cryoglobulinemia there have been more frequent reports. Ferri et al. evaluated the prevalence of neuropathy in 33 unselected patients with mixed cryoglobulinemia (age 45–71, 25 female). Using electrophysiologic assessment

including sensory nerve conduction velocities in combination with F wave (or the second of two voltages observed following electrical impulses applied to the distal aspect of a sensory nerve distribution) and H-reflexes (the reaction of the associated musculature following the application of an electrical stimulus to the distal region of a sensory nerve) [34]; they were able to detect neuropathy in 82% of subjects. They determined that F-wave alterations specifically were the most reliable technique to determine neurologic involvement. They then found a strong correlation with significantly elevated Cryocrit levels in patients with F-wave alterations ($p < 0.008$) and determined that hemorheological abnormalities seem to contribute to the pathogenesis of nerve injury [35].

3.3. Systemic lupus

Capillaroscopic evaluation was used to assess the association between Raynaud's phenomenon (RP) and systemic lupus erythematosus (SLE). In this work Pavlov-Dolijano et al. studied 79 total patients who suffered from SLE [36]. Forty four of them (43 women) with RP, and 35 (32 women) matched for age, sex, and disease duration with SLE without RP were studied. Central nervous system involvement and peripheral neuropathy were significantly more common in SLE patients with RP while Sjogren's syndrome was more common in SLE patients without RP. Of particular note was that enlarged capillaries ($p = 0.0482$), presence of avascular areas ($p = 0.0476$) and granular blood flow ($p = 0.0482$) were more common in patients with SLE who also suffered from RP, than in patients with SLE without RP.

In this work there is no causative relationship neuropathy and SLE with RP proffered, but it is a curious finding that micro-vascular dysfunction occurred in close correlation with neuropathic symptomatology.

3.4. Inflammatory enteropathies

Celiac disease is a chronic inflammatory enteropathy that has an associated neurologic disease in about 10% of all cases. These include psychiatric illness dementia, seizures, ataxia, but most often peripheral neuropathy. In this syndrome it is the celiac disease that may remain subclinical and it is the neuropathy that is the prominent clinical presentation. In this work nerve biopsy studies revealed loss of large diameter myelinated fibers, regenerative clusters of myelinated nerve fibers and a few isolated thinly myelinated fibers. There were no indications in the work that hemodynamic influences affected the development of the related neuropathy [37].

In 2005, Gibbons et al. presented a case series in which they described four patients who presented with presyncope and postural nausea. They stated that the four patients had biopsy proven celiac disease with dysautonomia present on autonomic evaluation, iterating the likelihood of neuropathy, autonomic or otherwise, being a possible presenting sign in patients with coeliac disease. Indeed the group stated that the patients comprised 2.4% of patients referred for autonomic testing in one yea. While this is greater than the reported prevalence of celiac disease in the United States of 0.71% (1 in 144) [38], it is consistent with the reported incidence found in peripheral neuropathy [37]. The relationship of hemodynamic alterations upon celiac disease- related neuropathy, as in the above work, remains unstudied.

3.5. Cobalamin deficiency-related neuropathy

Beitzke et al. investigated hemodynamic and autonomic nervous system dysfunction in patients with cobalamin deficiency, comparing autonomic responses to 60° passive head up tilting in controls vs. patients with the deficiency. Their work revealed that in the experimental or cobalamin deficient group, there was a significant fall in systolic blood pressure, a blunted fall of stroke index and cardiac index; and a lack of increase of total peripheral resistance. The results suggested that vitamin B_{12} deficiency causes autonomic dysfunction which may the cause for orthostatic hypotension [39]. In this description the causal or contributory mechanism is not definitive since any role blood pressure changes may have upon the initial development of the neuropathy is not asserted.

3.6. Transient receptor potential cation channel subfamily V and substance P receptor

In 2011, Fangyan et al. investigated the cardioprotection of methylcobalamin therapy against ischemia/reperfusion injury in isolated hearts of diabetic mice and the involvement of the transient receptor potential cation channel subfamily V (TRPV1). In their work they examined two models: the intact animal; and isolated hearts from streptozotocin (STZ)-induced diabetic murine models. In the isolated heart model they measured hemodynamic parameters and release of lactate dehydrogenase (LDH), calcitonin gene-related peptide (CGRP) and substance P (SP) in coronary effluent during reperfusion. The study revealed that in the isolated heart preparations the DM hearts that had received the methylcobalamin regimen yielded higher concentrations of SP in the coronary effluent ($p < 0.01$); higher expression of TRPV1 ($p < 0.01$); and higher expression of substance P receptor (SPR) in myocardium digestates. Normal hearts also yielded higher release of CGRP and SP in the effluent as well as higher expression of myocardial TRPV1, calcitonin receptor-like receptor (CRLR) and SPR than in DM preparations. They concluded that the cardioprotective effect of Methylcobalamin therapy in isolated DM murine hearts is related to the expression of TRPV1 and SPR [40].

3.7. Nerve and axonal regeneration

In murine models methylcobalamin has been shown to have central neuronal protection capabilities which include the promotion of injured nerve and axonal regeneration and protection of glutamate induced neurotoxicity [41–43]. However no direct relationship between peripheral neuropathy, hypotensive-ischemia, and glutamate has been studied to date. It has been speculated that in certain neuronal subpopulations such as hippocampal field CA-1 and neocortical layers 3, 5, and 6 which are characteristically destroyed after sub-maximal hypoxic–ischemic exposure that central neurotoxicity is the result of the endogenous exertion amino acid neurotransmitter, glutamate, released into the extracellular space. Whether this is a mechanism of neuronal protection in the periphery is unknown. Glutamate in the periphery has been shown to be important for sensory input transduction particularly along nociceptive pathways [44]. Complete characterization of the glutamatergic system in the peripheral nervous system is necessary, and its changes under varying pathological conditions are necessary. Clearly studies of any protective effects of Mecobalamin in the periphery need to be conducted before speculation upon any directed therapeutic intervention with methylcobalamin can be used.

3.8. Alcohol

3.8.1. Cardiac autonomic neuropathy and peripheral neuropathy

The link between alcohol and peripheral neuropathy has been described as recently as 2010, but the 1998 work by Agelink et al., emphasized the occurrence of autonomic neuropathy, and in particular a cardiac autonomic neuropathy (CAN) associated with chronic alcoholism [45]. This alcoholic CAN was also statistically significantly associated with peripheral neuropathy to the extent that the group reported that no evidence of CAN was found without a concomitant, clinically manifest peripheral neuropathy. The group also reported that the neuropathy was likely related to the total lifetime dose of alcohol as well as the duration of alcohol dependence; and that these components were the most important factors contributing to the pathogenesis of both the autonomic as well as the peripheral components of the disease. No distinct relationship of hypertension to the peripheral neuropathy *per se* was reported by any of these groups. Ayad et al. did assert, however, that the cardiac neuropathy/hypertension profile was consistent with a deleterious effect on vascular hemodynamics and structure [46]. This might suggest impairment of the microvasculature as a possible mechanism of nerve injury and subsequent peripheral, neuropathic processes.

3.9. Hypertension/hypotension (blood flow)

3.9.1. Hemodynamic correlates

Regarding hemodynamic correlates of blood pressure and neuropathy, Cho et al. referred to a cross-sectional study of age-associated peripheral neuropathy (AAPN) in which they determined that a history of hypertension was protective. In the work they designed, they collected baseline data from 584 patients in a longitudinal study of primary care patients 65 years of age and older. The patients were selected on the basis of having none of the 10 medical conditions known to cause peripheral neuropathy. The patients were assessed for any associations between peripheral neuropathy by examination and the following criteria: history of hypertension, number of anti-hypertensive medications, systolic blood pressure, diastolic blood pressure, pulse pressure and orthostatic hypotension. The group concluded that the negative correlation between hypertension and AAAPN was unexplainable. They noted that the positive association between pulse pressure and neuropathy in diabetic subjects supported findings from earlier studies and suggested AAPN and diabetic neuropathy may be distinct entities [47].

3.9.2. Cuban epidemic neuropathy

In a 1999 report, the Cuban epidemic neuropathy (CEN) outbreak which occurred from following an outbreak from January 1, 1992 through January 14, 1994 was described. During this health crisis, 50,862 Cuban residents were affected. The neuropathy included an optic form as well as a peripheral form with both types characterized by weight loss and easy fatigability [48]. In 2002, Gutierrez et al. studied autonomic cardiovascular reflexes in patients with CEN. They found that affected patients had significantly less heart rate variability during paced breathing. They reported that this suggested reduced cardiac parasympathetic innervation. While this study examined blood pressure changes in the setting of peripheral neuropathy no causative or influential relationship between the two was described [49].

3.9.3. Chronic venous insufficiency

Chronic venous insufficiency (CVI) as a correlate of peripheral neuropathy was examined in a 2000 study by Reinhardt et al. [50] This group compared 30 patients with CVI and 20 healthy controls using motor and sensory nerve conduction studies, vibration testing and thermotesting, the quantitative, sudomotor axon-reflex test, and Doppler flowmetry. In the CVI group distal motor latency of the peroneal nerve was prolonged ($p = 0.02$); there were increased limits for warm ($p = 0.016$) and cold detection ($p = 0.016$); and there was reduced vibration sense ($p = 0.008$). The group goes on to state that the results demonstrate a disturbance of A-alpha, A-beta, and A-delta fibers; as well as thermoafferent C-fibers. The mechanism of these disorders, they assert, is neural ischemia caused by a venous microangiopathy and increased endoneurial pressure.

3.9.4. Ischemic monomelic neuropathy

The relationship between chronic and critical leg ischemia was studied by Weinberg, et al. Nineteen patients suffering from chronic and critical leg ischemia were studied [51]. All patients experienced pain only 16% (3) were completely free of neuropathic symptoms. They concluded that there is a predominantly sensory neuropathy associated with chronic and critical limb ischemia, that measures of blood loss correlate with neurologic symptom scores and the suggest that the underlying pathophysiology is a distal axonopathy affecting nerve fibers of all sizes. This study implicates a perfusion dependent neuropathic pathogenesis exist in this syndrome.

3.9.5. Sympathetic denervation

The role of regional blood flow was further emphasized in a study that examined whether painful diabetic neuropathy is associated with abnormal sympathetic nervous function in affected limbs. Positron emission tomography (PET) scanning was used after intravenous injection of the sympathoneural imaging agent 6-[(18)F]-fluorodopamine to visualize sympathetic innervation and [(13)N]-ammonia to visualize local perfusion. Compared with non-neuropathic patients and diabetic patients with unilateral neuropathy in whom comparisons were made between the involved limb and the non-involved limb, PET scanning revealed decreased flow-corrected 6-[(18)F]- fluorodopamine derived radioactivity in patients with painful diabetic neuropathy as well evidence suggesting partial loss of sympathetic innervation [52].

The role of hypertension in the development of peripheral neuropathy was studied by Gregory et al. in 2012. They asserted that current rodent models did not adequately replicate all pathological features of diabetic neuropathy. Based upon this assertion they tested the hypothesis that combining hypertension with insulin-deficient diabetes produces a more pertinent model of peripheral neuropathy. In their work behavioral, physiological and structural indices of neuropathy were measured for up to 6 months in spontaneously hypertensive and age-matched normotensive rats with or without concurrent streptozotocin-induced diabetes. They found that hypertensive rats developed nerve ischemia thermal hyperalgesia nerve conduction slowing and axonal atrophy. In addition they observed the presence of thinly myelinated fibers with supernumerary Schwann cells which occur during cycles of degradation and production of myelin. The group also noted reduced levels of myelin basic protein. In streptozotocin-induced

diabetic rats similar findings were noted save for the absence of thinly myelinated fibers and the fact that there were normal levels of myelin basic protein [53]. Hence in the murine model, at least in the presence of diabetes, hypertension is not associated with a protective effect against the development of peripheral neuropathy seen in at least one human study [47].

3.9.6. Alpha lipoic acid

In an important work written in 2000, Haak et al. studied the beneficial effects of alpha-lipoic acid (ALA) is known to have on diabetic polyneuropathy. The work focused upon the effect of ALA on microcirculation in patients with diabetes mellitus and peripheral neuropathy. Two groups were compared: eight patients (age 60 ± 3 years) with diabetes of 19 ± 4 years who received a 6 week course of ALA, 1200 mg each day orally; and a second group of nine patients (age 65 ± 3 years) with diabetes of 14 ± 4 years duration. The groups had similar sex (~50%) and BMI (24.8 ± 1.3–23.6 ± 0.7 kg/m^2) distributions. The second group was studied before and after they had received 600 mg ALA or placebo intravenously over 15 minutes in order to investigate whether ALA has an acute effect on microcirculation. Capillary blood cell velocity was examined at rest and during post reactive hyperemia. They found that the oral ALA group showed a significant decrease in the time to peak capillary blood cell velocity (tpCBV). The intravenous infusion of ALA also decreased the tpCBV in patients with diabetic neuropathy. The group determined that in patients with diabetic polyneuropathy ALA improves microcirculation via an increased perfusion reserve. They asserted that their improvement in the symptoms of diabetic polyneuropathy may be occurring by virtue of improvements in microcirculatory blood flow at the level of the vasa nervorum [54].

3.9.7. Hypertension vs. hypotension

In a 2005 study Jarmuzewska et al. sought to determine which component of the blood pressure is responsible for a perceived link between hypertension and sensorimotor peripheral neuropathy [55]. To examine this relationship they took 55 consecutive outpatients with type II diabetes and measured blood pressure and 10 neurophysiological parameters: nerve conduction velocity at the median, ulnar, posterior tibial, and peroneal nerves; and sensory amplitude (AMP) and latency (LAT) at the median, ulnar and sural nerve. The results of this analysis showed that age, diabetes duration, systolic blood pressure and pulse pressure are negatively correlated with nerve function. Their regression analysis showed that after correction for age, disease duration, glycated hemoglobin, BMI, microalbuminuria, and SBP: PP was independently and negatively associated with nerve conduction and signal AMP; and positively correlated LAT. At least two considerations raised with this work: first there is no suggestion of any mechanistic relationship with the neurophysiologic changes and, second, there is presentation of the strength of the correlation between the acquired data and any regression line, i.e. R^2, despite the group reporting on what the analysis showed. The approach in the study, however, was important in that it specifically delineated quantifiable component s of nerve function that should be used in clinical models for future works on the relationship of flow and pressure dynamics on the development of neuropathic processes.

The relationship between hypotension and sensory motor peripheral diabetic neuropathy was further studied in a 2007 work by this same group [56]. Here they studied the connection

between cardiovascular risk factors, parameters of metabolic control and the presence of sensorimotor peripheral neuropathy. They examine blood pressure, glycated hemoglobin, lipid profile, and the presence of micro- and macro-vascular complications in 31 consecutive outpatients with type II diabetes age 60.7 ± 7.5 who had been diagnosed within 10 years of the study. Their work revealed that the prevalence of hypertension- defined as a blood pressure ≥ 140/90- was higher in sensorimotor peripheral diabetic neuropathy-positive patients. They went a step further and performed regression analysis on the date which revealed that after correction for age, gender, disease duration, glycated hemoglobin and serum lipids there was a correlation between hypertension and sensorimotor diabetic peripheral neuropathy. The group states that there is a strong association between hypertension and sensorimotor diabetic peripheral neuropathy but they report an R^2 – or the statistical measure of how close the data are to the fitted regression line- of 0.17 (17%), In other words the model explains relatively little of the variability of the data about the mean or the incidence of sensorimotor diabetic peripheral neuropathy. In this light the question of the relationship of hypertension with peripheral neuropathy, at least in the setting of type II diabetes remains equivocal. This is especially so in comparison to at least one study in non-diabetic patients which indicates that hypertension may be protective against the development of peripheral neuropathy [47]. In addition any question of a causal mechanism between hypertension and peripheral neuropathy remains unanswered.

Another attempt to correlate hemodynamics with peripheral neuropathy sought to use brachial-ankle pulse wave velocity, which is considered to be a valid marker of clinical atherosclerosis. The brachial-ankle pulse wave velocity is a measure of arterial stiffness and can be measured by peripheral tonometry, Doppler ultrasound and catheter tip manometry. Park et al. assessed 692 patients with type II diabetes (314 men, 376 women) with a mean age of 56.9 ± 10.9 years and a mean duration of diabetes of 7.9 ± 6.3 years [57]. The group chose the endpoints of neuropathic pain intensity on the numeric visual analog scale, the neurological assessment using ankle reflexes and the 10 g monofilament test; and the brachial-ankle pressure wave velocity. They found a positive correlation between the presence of peripheral neuropathy and maximal baPWV ($r = 0.127$, $p < 0.001$). After applying the independent t test the group then reported that the patients with peripheral neuropathy had higher maximal baPWV, systolic blood pressure, subject number of female sex; and older age compared with controls.

The role of hypertension in the development of peripheral neuropathy was not necessarily clarified in this work as the authors offered no such explanation, however the existence of peripheral artery disease as measured by baPWV and neuropathy raises the question of whether similar compliance changes occur in the microvasculature and specifically impact perfusion of peripheral nerves via the vasa nervorum.

The relationship between hypertension and diabetic peripheral neuropathy remains unclear and a consistent correlation (either positive or negative) between the two entities is yet to be found in the literature. Ozaki et al. in 2016 used a murine model to further examine this question [58]. Specifically their goal was to analyze the effects of hypertension on diabetic neuropathy. They studied morphologic features of peripheral nerves in rats with hypertension. They divided Male rats into two groups: alloxan-induced diabetic rats who received deoxycorticosterone acetate salt (DOCAS-salt) and non-diabetic rats who also received DOCA-salt. Sciatic, tibial (motor) and sural (sensory) nerves were then studied histomorphologically.

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Systolic blood pressure was maintained above 140 mmHg in both groups and endoneurial vessels in both groups showed endothelial hypertrophy and vessel lumen narrowing (**Figure 3**). However electron microscopic analysis revealed duplication of the basal lamina surrounding the endothelium and pericytes of the endoneurial vessels, a lesion the group stated that was more frequent and severe in the diabetic group (**Figure 4**). They also reported that on morphometric analysis of the tibial nerve there was a shift to smaller fiber and myelin sizes in the diabetic group than in the control group (**Figure 3**).

3.9.8. Superoxides

The role of superoxides in relationship to peripheral nerve damage caused by microvascular dysfunction in a murine model was examined in an important work by Jin et al. in 2012 [59]. In this study the group examined the effect of the sulfated polysaccharide complex sulodexide. This drug is known to induce acceleration of spontaneous fibrinolysis-thrombolysis of preformed thrombi [34]; to inhibit leukocyte activation and endothelial adherence [60]

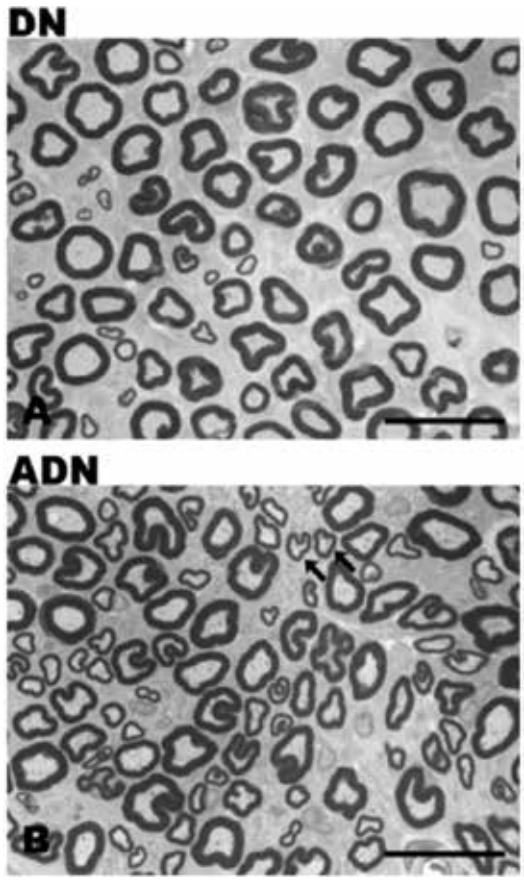

Figure 3. Representative sections of sural nerve in the control (A) and diabetic (B) groups. The small- sized myelinated fibers are increased in the diabetic group (arrows). Endoneurial fibrosis is observed in both groups (adapted from Ozaki et al. [58]).

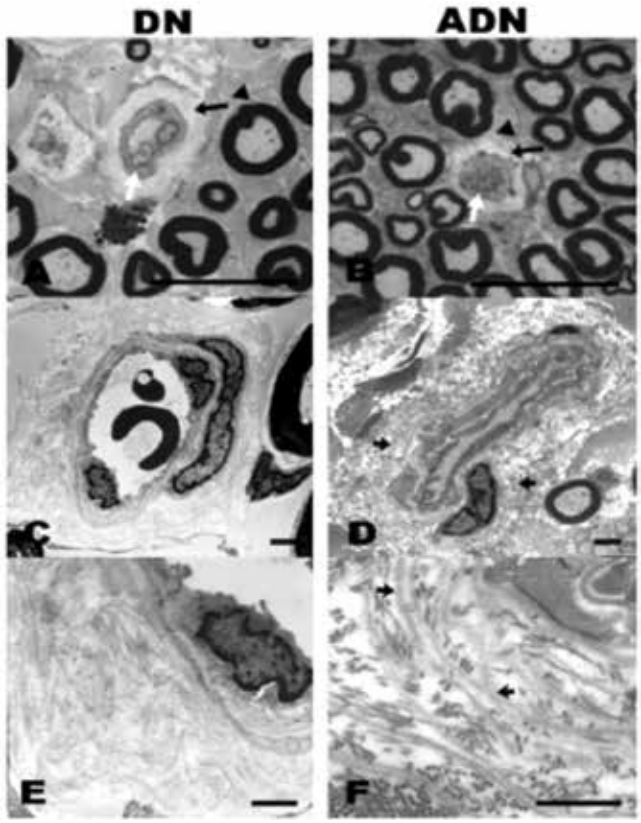

Figure 4. Representative sections of sciatic nerve in the diabetic (ADN) and control groups (DN). (A, B) in endoneurial vessels (white arrows), narrowing of the lumen with endothelial hypertrophy is observed in both groups. Both nerves show edema (black arrow) and fibrosis (arrowhead) in the endoneurium. (C, D) Electron microscopically, duplication of the basal lamina (arrows) surrounding the endothelium and pericytes of endoneurial vessels is seen in the ADN group. Many collagen fibers are also present around the vessels of both groups. (E, F) high magnification of **Figure 2** (C, D) has been performed. Duplicated basal laminae (arrows) of the diabetic group are also seen between collagen fibers, but in the DN group, edema is observed among collagen fibers (adapted from Ozaki et al. [58]).

and to protect endothelial integrity in the microcirculation [61]. The group divided female Sprague–Dawley rats into four groups normal, normal + SDX; DM; DM + SDX. They found that superoxide dismutase activity in the blood and sciatic nerve were increased significantly after sulodexide treatment. They also found that electrical current perception threshold was reduced, and that skin blood flow was improved in the DM + SDX group compared to the DM group ($p < 0.005$). They also found that that the mean myelinated axon area was significantly larger in the DM + SDX group vs. the DM group. The results of this work suggest not only the beneficial role of SDX in treating the peripheral neuropathy of DM but also that the drug may be useful in neuropathies of other origins. The work also supports the possible role of microneurovascular dynamics in the development of the disease.

3.9.9. Alpha adrenoceptor agonists

Small fiber neuropathy in diabetic patients treated with alpha-adrenergic agonists was the subject of a study by Schmiedel et al. in 2008 [62]. The emphasis of this work was on the impairment

of 0.1 Hz microvascular vasomotor. It tested the hypothesis that dermal vasoconstriction-induced microvascular oscillations are reduced in diabetic patients with peripheral and/or autonomic neuropath; and whether this method could be used as a non-invasive surrogate marker to assess diabetic small fiber neuropathy. The work examined four matched groups: diabetic patients without neuropathy; with peripheral neuropathy; with peripheral and autonomic neuropathy; and non-diabetic controls. Following iontophoretic administration of phenylephrine 0.1 Hz oscillations recorded at the foot were significantly attenuated in diabetic patients with peripheral and/or autonomic neuropathy compared to diabetic patients without peripheral neuropathy. Oscillation measures correlated significantly with all markers of peripheral neuropathy ($p < 0.001$) but not with markers of microvascular endothelial function of metabolic syndrome markers. In a logistic regression model, reduced microvascular oscillations at the foot were a strong predictor for the presence of peripheral neuropathy.

The findings of this work suggest that attenuation of oscillations, an indicator of vascular compliance, is reduced in the presence of diabetic neuropathy. The question then arises: is there a loss of such compliance in other or all described peripheral neuropathies. These studies are yet to be performed.

3.10. Uremia

Peripheral neuropathy in chronic kidney disease (CKD) or uremic neuropathy affects 90% of CKD patients [63]. There are multiple causes of CKD, the majority of which result from primary renal disorders. Among the CKD variants that occur as a complication of systemic disease, diabetes mellitus is the most common cause worldwide. It is noteworthy that regardless of the cause, patients afflicted with CKD have a high prevalence of neurologic complications. Initial work on the disease suggested that uremic neuropathy only occurred when the glomerular filtration rate (GFR) was consistently 12 mL/minutes. Recent studies, however, have demonstrated that uremic neuropathy occurs in about 70% of patients prior to their requiring hemodialysis [64]. The characteristic symptoms, which include pain, loss of sensation, and weakness, can be disabling. Uremic neuropathy commonly affects large motor neurons and sensory fibers. Small nerves are commonly involved as well. Early signs and symptoms include distal sensory loss and reduced tendon reflexes in the lower extremities. As the neuropathy progresses, the loss of sensation extends proximally in the lower extremities. Similar symptoms can occur in the upper extremities. In the advanced stages, motor nerves of the lower extremities are affected leading to muscle atrophy and resulting weakness. The effects of systemic uremia on peripheral nerves can be demonstrated by the generalized decrease in conduction velocity in both motor and sensory nerves. This is caused by structural changes along the length of the peripheral nerves. In addition to structural changes, there is likely an unknown uremic toxin that is neurotoxic.

Studies have identified several compounds that are now considered to be possible neurotoxins. Creatinine, urea, uric acid, guanidine, methyl guanidine, guanidinosuccinic acid, oxalic acid, phenols, aromatic hydroxyacids, indicant, amines, myoinositol, beta-2 microglobulin, parathyroid hormone, amino acids, and neurotransmitters all fall into this group. None of these compounds, however, have moved beyond the speculative consideration and been definitively proven to be a cause of peripheral neuropathy.

Recent evidence suggests that hyperkalemia plays a major role in uremia related peripheral neuropathy. Hyperkalemia has been shown to cause axonal dysfunction in a dose-dependent

manner. This dysfunction can be reversed with the treatment of hyperkalemia suggesting that maintaining normal potassium level in CKD patients can help prevent uremic peripheral neuropathy [65]. There is no evidence to suggest that normalizing serum potassium levels can reverse the peripheral nerve dysfunction in patients with existing uremic peripheral neuropathy at any stage. It is known that uremic toxins are likely to be direct or indirect causes of central nervous system neurodegeneration. Uremia indirectly contributes to systemic inflammation, endothelial dysfunction and atherosclerosis leading to neurodegeneration and cognitive dysfunction. Several compounds including uric acid, indoxyl sulphate, rhocresyl sulphate, interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha have been suggested as likely contributors to the development of neurodegeneration [66]. Interestingly, crystalin-C has recently also been attributed to neurodegeneration through amyloid plaque formation [67]. The possible direct causes of neurodegeneration have been mentioned previously. Intuitively, it is possible to suggest that neurodegeneration directly or indirectly, centrally and/or peripherally is multifactorial. It involves multiple causative agents that may act either as direct neurotoxins or via the induction of systemic inflammation, endothelial dysfunction, and atherosclerosis. Each of these processes may lead to the disruption of pressure-dependent blood flow, and ultimately lead to neuropathy and cell death.

3.11. Chemotherapeutic agents

Chemotherapy-induced peripheral neuropathy (CIPN), as the name implies, occur in oncology patients who have been exposed to neurotoxic chemotherapeutic agents. CIPN is debilitating and often develops after several treatments in a dose dependent fashion. Interestingly, a few of the newer chemotherapeutic agents can cause CIPN in an idiosyncratic way unrelated to the accumulated dose of the agents. In a 2007 work Kannarkat et al. reviewed the literature regarding complications of common chemotherapeutic agents and chemotherapeutic agents that had been recently developed [68]. While their main emphasis was upon the cognition-impairing effects of the therapy they also looked at the occurrence of neuropathic pain with the drug Bortezomib which was the first therapeutic proteasome inhibitor to be used in humans. The group found that the drug has a propensity toward causing a largely sensory but reversible peripheral neuropathy. The group found from the literature that the infusion of magnesium and calcium pre- and post- oxaliplatin infusion reduces the neuropathy associated with this specific drug but that it may actually interfere with clinical response to oxaliplatin. They stated that no other known interventions at the time reduced the incidence or severity of neuropathy related to platinum compounds, taxanes (toxoids), or thalidomides. They did suggest that regional neural blood flow, DNA damage, mitotic dysfunction, defects in neural repair, and oxidative stress may play roles in the effects of chemotherapeutic agents upon the nervous system.

CIPN affects approximately 30 to 40% of patients receiving neurotoxic chemotherapeutic agents [69]. Common groups of agents with established associations with CIPN are platinum based drugs, vinca alkaloids, taxanes (toxoids), thalidomide, and proteasome inhibitors. Cyclophosphamide, methotrexate and immune check point inhibitors have also been reported to cause CIPN. CIPN is often caused by primary direct neurotoxic effect on the neurons often with a predilection for sensory over motor and autonomic neurons causing anatomic and/or physiologic changes. Symptoms are likely amplified by hyper-excitability and central sensitization. The anatomic changes are mainly targeted at the dorsal root ganglion neurons or

their axons leading to peripheral sensory loss, ataxia, and pain. A significant exception to this mechanistic tendency of chemotherapeutic agents is the likely mechanism by which platinum compounds cause neuropathy. This is based upon the fact that, typically, only a sensory neuropathic component is observed. Regarding thalidomide and its newer analogues, recent evidence of its toxicity pathway suggests that anti-angiogenesis may play a significant role in the cause of CIPN. Anti-angiogenesis may not be unique to the thalidomide class but indeed may contribute to a common pathway to CIPN for all chemotherapeutic agents [70, 71].

Platinum-based chemotherapeutic agents commonly used include cisplatin, oxaliplatin, and carboplatin. Of these, the most toxic compound is cisplatin. All of the platinum-based chemotherapeutic agents cause permanent sensory CIPN. They are believed to inflict damage upon the dorsal root neurons. This is the result of adduct formation with nuclear and mitochondrial DNA which ultimately leads to cellular apoptosis. There is also evidence to suggest that cisplatin-linked anti-angiogenesis causes peripheral neuropathy [71]. Direct mitochondrial damage also occurs and is postulated to the coasting phenomenon in which the symptoms of CIPN continue to worsen several months after the discontinuation of therapy [72].

The role of platinum-based chemotherapeutic agents in the development of neuropathy was evaluated in a prospective study by Boogerd et al. in which the group examined the occurrence and degree of central peripheral and autonomous neuropathy. Twelve patients were examined before, during and after initiation of cisplatin treatment. Their evaluations included neurologic examination, nerve conduction studies of median and peroneal nerves, and short latency somatosensory evoked potentials (SSER) after median and tibial nerve stimulation. They noted that SSER appeared to be the most sensitive method for the detection of peripheral nerve impairment [73].

In 2011, Cunningham et al. stated that chemotherapy induced peripheral neuropathies (CIPN) developed from unknown mechanisms but that symptoms could be reduced by manual therapy (massage) implying that digital augmentation of blood flow may provide symptomatic relief from neuropathic pain [74].

Yeo et al. in 2016, using a murine model, showed that clonidine dose-dependently reduced oxaliplatin-induced allodynia and spinal p–p 38 mitogen activated protein kinase (MAPK) expression. When given in combination with the MAPK inhibitor SB203580, reduced dose clonidine decreased allodynia without significant, undesirable motor or cardiovascular effects [75].

3.11.1. Antimicrotubule agents

This class of chemotherapeutic agents includes taxanes (or toxoids), vinca alkaloids, and the newer agents, eribulin, ixabepilone, brentuximab, vedotin, and ado-trastuzumab emtansine. Taxanes, paclitaxel, docetaxel, and cabazitaxel are used commonly and cause painful, dose and length-dependent sensory neuropathy. The mechanism for this is likely due to the ability of taxanes to cause target interference with microtubule-based axonal transport function [76]. Vinca alkaloids, vincristine, vinblastine, vindesine, and vinorelbine destabilize microtubule formation interfering with axonal transport and mitochondrial function. The compounds can lead to length-dependent sensory neuropathy with some motor neuron involvement. The degree of neuropathy may be long term or permanent. Epothilones, eribulin and ixabepilone, have the same mechanism of action as taxanes, causing axonal sensorimotor CIPN [77].

Brentuximab vedotin and ado-trastuzumab emtansine are biologic hybrid agents created by the conjugation of tumor specific antibody to a chemotherapy agent. They both interfere with microtubule function and the use of these agents results in a high incidence of CIPN.

In a 2000 study Ekholm et al. *examined* the taxoid chemotherapeutic agent Paclitaxel in order to determine if it changed cardiovascular regulation in breast cancer patients previously treated with anthracyclines. They concluded that Docetaxel treatment did not cause deterioration of vagal cardiac control in breast cancer patients after exposure to epirubicin. They also determined that the observed changes in blood pressure response suggested that docetaxel changes sympathetic vascular control; however the changes appeared to be related to changes in cardiovascular autoregulation as opposed to neuropathic changes in the peripheral sympathetic fibers [78].

Later, in 2007, Kirchmair and his group studied Paclitaxel as used in the treatment of breast, lung, and ovarian cancers; and thalidomide as used to combat multiple myeloma and other bone marrow cancers [70]. Again, the rationale for the study was the dose limiting effect of the development of peripheral neuropathy when these drugs are used. The group hypothesized that the toxic neuropathies resulting from the destruction of vasa nervorum and that the neuropathy could be reversed by administering an angiogenic cytokine. The group used a murine model and employed intramuscular gene transfer of naked plasmid DNA encoding VEGF-1 administered in parallel with Taxol injections. They found that in this setting there was complete inhibition of nerve function deterioration and inhibition of peripheral nerve vasculature diminution. A similar result was seen when the study was repeated using thalidomide. The work iterates the implication of microvascular damage as the basis for toxic neuropathy and, again, regional blood flow and vascularity appear to be critical components in the development as well the prevention of peripheral neuropathy.

Gracias et al. in 2011 studied peripheral neuropathy secondary to paclitaxel exposure in a murine model [79]. Paclitaxel targets tubulin and stabilizes the microtubule polymer and protects it form disassembly and blocks mitotic progression at the spindle checkpoint which delays the onset of anaphase and triggers apoptosis [80]. In their work, Gracias et al. dosed male Sprague–Dawley rats with 1 mg.kg paclitaxel for four doses over 8 days and examined hind paw vasodilation as an indirect measure of calcitonin gene-related (CGRP) release. When compared to rats that were injected only with vehicle, capsaicin- or electrical stimulation of the sciatic nerve- induced vasodilation, paclitaxel-treated rats demonstrated significantly attenuated vasodilation. Paclitaxel did not affect direct vasodilation induced by intradermal injection of methacholine or CGRP which demonstrated that blood vessels' ability to dilate remained intact. These results suggest that paclitaxel affects the peripheral endings of sensory neurons to alter transmitter release, and this may contribute to the symptoms seen in neuropathy. Further we may possibly query whether the diminished vasodilation from more central stimulation may inhibit blood flow to the degree that consistent vasa nervorum- mediated perfusion becomes impaired leading to peripheral nerve compromise and subsequent peripheral neuropathy.

3.11.2. Proteasome inhibitors

The proteasome inhibitor, bortezomib, causes length-dependent small fiber neuron axonal sensory neuropathy. Fortunately, it is a reversible phenomenon. Additionally, bortezomib may also cause severe immune-mediated polyradiculoneuropathy in some patients. Newer generation

proteasome inhibitors, carfilzomib and ixazomib, have a lower incidence of CIPN compared to bortezomib [81, 82]. The mechanism by which proteasome inhibitors cause CIPN is thought to be the result of their effects on the microtubules and mitochondria of sensory neurons. This effect results in decreased axonal transport and function [83, 84].

Bortezomib is used in the treatment of multiple myeloma and is known to result in peripheral neuropathy [85], Tsukaguchi et al. [86] employed the use of lafutidine an H2-blocker with gastroprotective activity which is believed to function via a similar mechanism as capsaicin, i.e., increasing mucosal blood flow via capsaicin-sensitive afferent neurons, and selective blockade of afferent sensory neurons. An example of this function is the ability of lafutidine to reduce the pain of glossodynia and taxoid-induced peripheral neuropathy [86].

Peripheral neuropathy (PN) caused by bortezomib was studied in eight patients twice a week for 2 weeks followed by 1 week without treatment for up to four cycles. Lafutidine was administered orally at 10 mg twice daily. The total occurrence of PN was four out of the eight patients. They found from this limited study that although the total occurrence of PN after the first course and in no cases was bortezomib treatment discontinued because of PN. It may be speculated that lafutidine is useful for the amelioration of bortezomib-induced PN. Bortezomib is a 20S proteasome complex inhibitor that acts by disrupting various cell signaling pathways leading to cell cycle arrest, apoptosis, and inhibition of angiogenesis. Bortezomib causes mitochondrial changes resulting in swollen and vacuolated mitochondria in axons, opening of mitochondrial permeability transition pore (mPTP) with release of intracellular calcium; and activation of caspase and apoptotic pathways [87]. The anti-angiogenesis activity of this drug may have implications upon the pressure and flow development component of peripheral neural blood supply and the evolution of neuropathic changes.

Speculation upon the role of a capsaicin-like intervention in this neuropathy must of necessity consist of consideration of interactions at a number of sites in the molecular pathways of nerve injury and death. Studies, then, are needed to dissect these interactions and shed light upon the effect of this treatment.

3.11.3. Antiretroviral chemotherapeutic agents

Patients treated with antiretroviral medications of the nucleoside analogue reverse transcriptase inhibitors (NRTIs) class of drugs can develop myopathy and neuropathy of varying severity after prolonged therapy with the neuropathy characterized as painful, sensory and axonal [88]. NRTIs cause mitochondrial DNA (mtDNA) dysfunction and impaired oxidative phosphorylation. There is evidence that the resultant mitochondrial toxicity is due to a new category of acquired mitochondrial toxins, azido groups that compete as substrates of DNA pol-gamma and terminate mtDNA synthesis and thus lead to axonal degradation [89].

In a 2005 case report Fodale et al. *describe* a fatal exacerbation of peripheral neuropathy in which iatrogenic mitochondrial damage occurred. They describe a 57 year old man with mild neuropathy with hepatitis B and C virus treated with the antiretroviral lamivudine 300 mg per day. The causal relationship was implied when at 3 months of therapy he presented with dysphoria and progressive muscle weakness. He subsequently developed quadraparesis, acute respiratory failure and sudden cardiac arrest with successful resuscitation. The lamivudine was discontinued

and respiratory capacity improved. The patient subsequently died suddenly despite hemodynamic, ventilator and metabolic support. Electrophysiological studies prior to death revealed sensory-motor axonal neuropathy. Biochemical and mitochondrial DNA molecular genetics suggested possible widespread iatrogenic mitochondrial damage. The group speculated that mtDNA dysfunction could be a potential cause of the sudden cardiac arrest [90].

3.12. Antibiotics and antifungals

Antibiotics are commonly used agents in both inpatient and outpatient settings. They are generally well tolerated but may cause peripheral neuropathy in idiosyncratic as well as dose-dependent fashions. The incidence of peripheral neuropathy associated with antibiotics is drug dependent and is relatively rare compared to the incidence seen with chemotherapeutic agents. It has been demonstrated that clinically appropriate doses of bactericidal antibiotics can cause mitochondrial dysfunction that leads to leakage of toxic reactive oxygen species (ROS) from the mitochondrial electron transport chain (ETC) in mammalian cells [91]. The ROS can interact with cellular components such as lipids, protein and DNA. The end result is oxidative stress with subsequent tissue damage. The oxidative stress produced by bacteriostatic antibiotics is significantly less. Similar to the chemotherapeutic agents, antibiotics have been shown to inhibit angiogenesis [92], which has been proposed as a major mechanism of chemotherapeutic-related neurotoxicity and peripheral neuropathy [70]. The antibiotic classes that are known to cause peripheral neuropathy are: aminoglycosides, tetracyclines, fluoroquinolones, oxazolidinones, and polymyxins. Clinical observations however suggest that the malady is not limited to these antibiotic groups alone.

3.12.1. Aminoglycosides

The ototoxicity associated with aminoglycosides is well described. The role of this antibiotic in causing peripheral neuropathy and encephalopathy is less commonly discussed. The mechanism leading to peripheral neuropathy is unclear. Gentamycin has been linked to peripheral neuropathy and microscopic examination of involved neural tissue have reveals lysosomal abnormalities that as of yet have no clear cause [93]. Current evidence appears to suggest that this group of antibiotics causes nerve damage via the activation of NMDA receptors and subsequent release of oxidative radicals. It is postulated that the excitotoxicity activation of NMDA receptors within the cochlear leads to the formation of ROS causing ototoxicity [94, 95]. Intrastriatal neomycin leads to gliosis. It is noteworthy that this effect is attenuated in the presence of NMDA antagonists. Neuromuscular blockade, commonly associated with aminoglycosides, is a temporary form of peripheral neuropathy. These agents inhibit the quantal release of acetylcholine pre-synaptically and bind to the acetylcholine receptors post-junctionally at the neuromuscular junction causing weakness.

3.12.2. Tetracyclines

Tetracyclines have been associated with neuropathy of the cranial nerves [96]. However, the cause and incidence are unclear.

3.12.3. Fluoroquinolones

Fluoroquinolones have been known to cause peripheral neuropathy. Oral fluoroquinolones are associated with an increased risk of developing peripheral neuropathy of up to 30% [97], and an overall incidence of 1% of developing this disorder [98]. Of all the cases of fluoroquinolones associated peripheral neuropathy, 9% of these patients had Guillain-Barre syndrome [98]. The three fluoroquinolones commonly implicated in peripheral neuropathy are ciprofloxacin, levofloxacin, and moxifloxacin [97, 98]. Fluoroquinolones are associated with neurotoxicity of central nervous system possibly through their inhibition of GABA receptors [99]. Peripheral nerves also express GABA receptors. Whether the interaction of fluoroquinolones with GABA receptors of peripheral nerves or Schwann cells or whether it is a combination of an interaction with both classes of cells that leads to peripheral neuropathy still remains unknown.

3.12.4. Oxazolidinones

Oxazolidinones is a unique class of antibiotics that is completely different from any other antibiotic group. The only oxazolidinone available for clinical use is linezolid. Little is known about the mechanism by which linezolid causes peripheral neuropathy or the incidence of this peripheral neuropathy. There are reports of linezolid causing Bell's palsy and optic neuropathy [100, 101]. and there is at least one report that details four cases of linezolid causing peripheral neuropathy with concomitant use of a selective serotonin re-uptake inhibitor (SRI) [102]. In a retrospective analysis of 75 patients receiving treatment with a combination of six drugs including linezolid and pyridoxine, 13% of the patients were found to have sensory peripheral neuropathy [103].

3.12.5. Metronidazole

Metronidazole has been reported to cause both motor and sensory peripheral as well as optic and autonomic neuropathies [104–107].. The incidence of peripheral neuropathy is unknown and appears to be dose dependent. The precise mechanism of metronidazole causing neuropathy is unknown. It has been suggested that metronidazole-induced vasogenic edema leading to axonal swelling is a likely cause [108].

3.12.6. Polymyxins

The polymyxins, polymyxin B and colistin have an approximately 7% incidence of paraesthesias and polyneuropathy in treated patients [109]. It appears that the route of administration correlates with the severity of the incidence of neuropathy. Intravenous administration of polymyxin B incidence of neuropathy is 27% as compared to 7.3% for the intramuscular route [110]. Neurotoxicity is also dose dependent and there is a sex predilection with females having a higher rate of neurotoxicity as compared to males. The mechanism of neurotoxicity is postulated to be the interaction of polymyxins with neurons due to their high lipid content [111].

3.12.7. Nitrofurantoin

Nitrofurantoin has been implicated as the cause of sensorimotor polyneuropathy in pediatric patients, especially those with a history of renal insufficiency. This manifests as paresthesia and dysesthesia in the lower extremities [112–114]. The incidence is estimated to be about 0.0007% [115]. The precise mechanism of the polyneuropathy is unknown.

3.12.8. Isoniazid

Isoniazid causing dose-dependent, reversible sensorimotor peripheral neuropathy is a well-known phenomenon that is preventable with the administration of pyridoxine. The incidence of peripheral neuritis is from 6% to approximately 20% in patients taking exposed to a dose of 6 mg/kg daily [116, 117]. There are also reports of isoniazid in combination with ethambutol causing severe but reversible optic neuritis [118]. The mechanism by which isoniazid causes peripheral neuropathy is unknown but it has been suggested to relate to isoniazid-induced pyridoxine deficiency. The complex relationship between isoniazid and pyridoxine is unknown. In adults, pyridoxine supplement is recommended with isoniazid treatment. However, in the pediatric population, pyridoxine prophylaxis with isoniazid is not necessary [119].

3.12.9. Triazole antifungals

The triazole antifungal class of drugs includes itraconazole and voriconazole, which are currently in clinical use. These drugs associated with an increased risk of development of peripheral neuropathy. The incidence is estimated to be approximately 10%, and the symptoms are partially or fully reversible after cessation of therapy [120]. The precise cause remains unknown.

3.13. Miscellaneous

3.13.1. Oxidative stress

The role of thiobarbituric acid reacting substances (TBARs) measure of lipid peroxides in the neural blood flow abnormalities associated with diabetes and its metabolic changes in peripheral neuropathy was studied in 2005 by Migdalis et al. In this work 77 patients with type II diabetes (39 neuropathic and 38 non-neuropathic) and 38 control patients were studied. The neuropathic study group had significantly lower levels of TBARs, 3.5 μmol/L (2.2–5.6, $p < 0.05$) compared to controls, 4.5 μmol/L (3.08–8.05, $p < 0.001$) and to diabetics without neuropathy 4.9 μmol/L (3.09–8.05, $p < 0.001$). In the neuropathy group there was a negative correlation between the score for nerve dysfunction with TBARs level, $r = -0.42$, $p < 0.01$.

This finding was counter intuitive since lipid peroxide levels or TBARs are typically thought to be elevated in disease states such as atherosclerosis and diabetes (Yagi, 1998). The implications of this study are unclear with the authors asserting that TBAR levels in patients with diabetic neuropathy are "abnormal" but do not offer an explanation of the negative correlation between the score for nerve function with the TBAR levels.

We submit that further studies need to be undertaken in order to clarify this relationship. Based on contemporary works in murine models a most reasonable sequel to this study

would be follow-up examinations of TBARs and anti-oxidant therapies in these same *in vivo* diabetic neuropathy preparations [121].

The oxidative stress and pro-inflammatory processes which contribute to vascular complications including endothelial dysfunction and peripheral neuropathy in diabetes mellitus was examined in a 2006 study by Nangle et al.. [21] In this work the group administered eugenol – which is known to have antioxidant and anti-inflammatory properties especially in the inhibition of lipid peroxidation [122] – to streptozotocin induced diabetic rats. The group analyzed endoneurial blood flow reduction; gastric fundus maximum nitrergic nerve-mediated relaxation reduction; and maximum endothelium-dependent relaxation reduction in renal artery rings all in diabetic animals. Eugenol significantly improved or completely reversed each of these reductions but did not affect diabetes-increased sensitivity to phenylephrine-mediated contraction. Nevertheless the study demonstrated that both vascular as well as neural complications of experimental diabetes are improved by the antioxidant/anti-inflammatory agent eugenol and reinforces the argument for the role of pressure-flow perfusion dependence on the development of oxidative stress-related peripheral neuropathy.

3.13.2. Eosinophilic granulomatosis with polyangiitis (EGPA)

In 2015 Boubabdalloui et al. discussed a case report of eosinophilic granulomatosis with polyangiitis (EGPA) and described a peripheral vasculitis in a 21 year old man who presented with an associated peripheral neuropathy [123].

3.13.3. Nitric oxide

Some studies have suggested a key role of nitric oxide in development of injuries resulting from malfunction of the microvasculature as a result of neuropathic peripheral nerves. These neuropathies may be age- or disease- related. In a 2002 article Minson et al., examined thermally induced cutaneous vasodilation capacity (% CVC max; 28 mM nitroprusside infusion) in response to the nitric oxide inhibitor NG-nitro-L-arginine methyl ester (L-NAME) which was infused throughout the protocol [124]. The study compared 2 groups using microdialysis fibers placed in the forearm skin of 10 young subjects (age 22 ± 2 years) and 10 older subjects (77 ± 5 years) with skin blood flow subsequently measured by laser-Doppler flowmeters. The protocol entailed the heating of both sites to 42°C for approximately 60 minutes with data expressed as a percentage of maximal vasodilation. The work revealed that local heating before L-NAME infusion resulted in a significantly reduced initial peak, 61 ± 2% CVC max, in younger subjects vs. 46 ± 4% CVC max in older subjects; and a reduced plateau CVC in younger subjects (93 ± 2% CVC max) as well as in older subjects (82 ± 5% CVC max). When the nitric oxide synthetase (NOS) inhibitor was infused following 40 minutes of heating CVC declined to the same value in the young and older adults. They concluded from the work that the overall contribution of nitric oxide to the plateau phase of the SkBF response to local heating was less in the older subjects. Further they concluded that age-related changes in both axon reflex-mediated and NO mediated vasodilation contributed to attenuated cutaneous vasodilator responses in the elderly [124]. In 2010, Fromy et al. focused upon mechanosensitivity and vasodilation or pressure-induced vasodilation (PIV) or the dilation of the cutaneous microvasculature when a non-nociceptive external pressure is locally applied to

the skin [125]. PIV is mediated by mechanical stimuli (pressure) applied to sensory C-fibers which subsequently release neurotransmitters that cause the release of endothelial factors which cause smooth muscle relaxation of the cutaneous microvessels. This response has been documented in both murine as well as in human models. Based on earlier studies in which this group demonstrated that PIV is altered in the skin of old mice without neuropathy, the group then hypothesized that older humans would have reduced PIV as well. Their study examined two age groups: older subjects (60–75 years) and younger subjects (20–35 years). They determined that there were statistically significant changes in percentage vasodilation in response to local pressure application among all (young, non-neuropathic older, and neuropathic older) groups (**Figure 5**).

The group states that there is altered physiological ability to protect the skin against localized in 60–75 year old subjects and that older subjects who present with a severe sensory deficit, i.e., neuropathy are particularly at risk for pressure ulcer occurrence because of a loss of local PIV [125]. One important aspect of this work is that it implies a role of nitric oxide both from this group's previous murine model work and implications from related thermosensitivity studies by Minson et al… [124] Another important aspect is the possibility that nitric oxide may play a role in pressure-induced vasodilation. Indeed some low-threshold mechanoreceptors as well as some thermoreceptors fall into the class of unmyelinated C-fibers which release the aforementioned neurotransmitters that initiate the cascade which may result in the expression of nitric oxides and the resultant microvasodilation.

3.13.4. Environmental toxins

Other toxicities have been described as causing neuropathy. In a 1999 report, Fung et al., described the development of severe neuropathy in a 57-year-old man who developed signs and symptoms of peripheral following a 2-day exposure to styrene. During this time the patient had been applying the styrene this time applying the styrene which was contained in a fiberglass resin to the

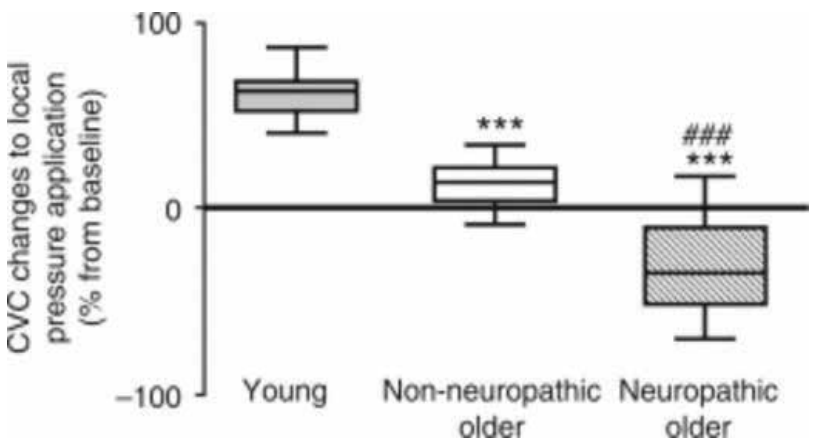

Figure 5. Percentage of vasodilation in response to local pressure application (4.2 kPa) in young ($n = 12$), non-neuropathic older ($n = 12$), and neuropathic older ($n = 10$) subjects. Statistically significant changes relative to young subjects ($^{***}p < 0.001$) and non-neuropathic older subjects ($^{###}p < 0.001$) CVC is cutaneous vascular conductance. The line drawn across the box is the median. The lower and upper edges of the box are drawn at the first and third quartiles, respectively. The whiskers represent the maximal and minimal value (adapted from Fromy et al. [125]).

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inside of the septic tank. The neuropathy was documented by signs and symptoms consistent with a neuropathic process which was later confirmed by nerve conduction studies [126].

Abnormalities of peripheral nerves have also been observed as a result of exposure to the highly toxic industrial cleaner and insecticide, carbon disulfide. In a 2004 work, Huang et al. examined the effects of CS on the central and peripheral nervous system 3 years following cessation of exposure. They found that abnormalities of the PNS persisted and included clinical symptoms and electrophysiological findings. They also determined that central nervous system changes occurred and persisted with brain magnetic resonance images showing changes in the basal ganglia and the subcortical white matter that were suggestive of vascular events, particularly in the small vessel. The group also noted in one patient diffuse cerebral hemispheric demyelination. In their conclusion they stated that the cardiovascular system involvement may be due to thrombotic effects as opposed to atherogenic effects [127]. This raises the question of the genesis of the demyelination seen in the central nervous system. Was this the result of microangiopathy, and if so was there a similar genesis in the peripheral nerves with demyelinative changes there as well? No microscopic exams of the peripheral nerves were reported at that time, which leaves perfusion dependence of the development of peripheral neuropathy subject to speculation which necessitates further study.

4. Conclusion

The causes of peripheral neuropathy are many as we have encountered in the preparation of this chapter. Perhaps the most pronounced theme occurred at the molecular level where it appeared that oxidative stress and angiogenesis played possibly the most prominent roles in the development of perfusion dependent peripheral neuropathy. It is at this level that we believe extensive research must be performed both at the bench as well as at the bedside in order to find possible correlation with any basic science breakthroughs. It is certainly apparent to our group that interventions specifically at those points, i.e., control of the production and removal of free radicals as well as the manipulation of differential angiogenesis are essential. Completion of the latter task can only be described as daunting since many disease processes including several malignancies are promoted by angiogenesis. To differentially promote neuroprotective angiogenesis while inhibiting pathogenic angiogenesis and controlling concomitant beneficial perfusion pressures may lead to optimal results as we seek to alleviate suffering from peripheral neuropathy.

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Chapter 4

Hypertension and Sleep Apnea

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Additional information is available at the end of the chapter

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Abstract

Diagnosis and treatment of comorbid conditions in hypertension are essential for efficient blood pressure control and for decreasing adverse clinical events and mortality. Sleep apnea, mainly its obstructive form, has a high prevalence both in the general population and in hypertensive patients, the main reason being the worldwide epidemic of obesity. This chapter summarizes the principal issues related to hypertension-sleep apnea relationship: definition of terms, epidemiological data and evidences, clinical manifestations of sleep apnea, pathophysiological background of the adverse effects of sleep apnea on the cardiovascular system, screening and definitive diagnosis, and the effects of specific and nonspecific sleep apnea interventions on hypertension.

Keywords: hypertension, sleep apnea, pathophysiology, diagnosis, treatment

1. Introduction

Cardiovascular and non-cardiovascular comorbidities are frequently present in the setting of hypertension. Usually, they influence adversely the clinical course and treatment; thus, their identification (diagnosis) and management is mandatory. In this regard, sleep apnea, due to its high prevalence and the multiple ways it could affect the patients, is considered one of the most important non-cardiovascular comorbidities in hypertension [1, 2].

2. Definitions, quantification of sleep apnea

Sleep apnea (SA) is a sleep-related breathing phenomenon and consists of the involuntary cessation (or near cessation, >90%) of airflow to the lungs for at least 10 seconds. SA takes part

from the large family of sleep disorders, being the most important manifestation of sleep-related breathing disorders ("sleep disordered breathing"). The latter entity also comprises the sleep-related hypoventilation syndromes, their most frequently occurring form, the obesity hypoventilation syndrome, being also present (with or without SA) in some patients with hypertension and/or metabolic syndrome [3, 4].

While apnea is the most characteristic and important phenomenon, there also exist other respiratory events related to sleep, which have to be considered. Hypopnea represents an at least 30% reduction of airflow for 10 seconds from the pre-event baseline, associated with 3% oxygen desaturation and/or an arousal signal on the EEG, or, alternatively, a 4% oxygen desaturation (the arousal being not mandatory in this case) [3, 4].

Respiratory effort-related arousals (RERAs), lasting at least 10 seconds, are induced by airflow limitation (increased upper airways resistance), which do not fulfill the criteria for apnea or hypopnea. In fact, increased upper airways resistance, hypopnea, and apnea represent a continuum and denote progression of the of the sleep-related upper airways obstruction [3, 4].

The most used parameter for the quantification of SA is the so-called apnea-hypopnea index (AHI), which represents the number of (apneas + hypopneas)/hour of sleep and is determined more exactly by polysomnography (PSG). The AHI is <5 normally, and the SA is considered significant if the AHI is ≥15. An AHI ≥ 30 heralds a severe SA. Another approach of quantification uses the respiratory disturbance index (RDI), which represents the number of (apneas + hypopneas + RERAs)/hour of sleep. In the case of home sleep apnea testing (HSAT), the devices used are not capable of EEG recording (which identifies the sleep phases and arousals); thus, the American Academy of Sleep Medicine (AASM) recommends the term "respiratory event index" (REI) instead of AHI or RDI. In this case, the number of sleep hours is replaced by the number of recording hours. On the other hand, different indices of the degree of hypoxemia occurring during sleep could also be calculated—hypoxemic burden, oxygen desaturation index, average oxygen saturation, etc. [3–6].

Obstructive sleep apnea (OSA) is a form of SA, when the lack of airflow is caused by the collapse of the upper airways (mainly at the level of oropharynx) and the—inefficient—respiratory movements are maintained during apnea/hypopnea (similarly to forced inspiration against a closed glottis = Müller's maneuver). An arousal reaction with or without awakening re-establishes the normal breathing. OSA is the typical form of SA encountered in the setting of hypertension.

In the case of central sleep apnea (CSA), the malfunction of the respiratory center and the lack of efferent impulses to respiratory muscles cause the airflow cessation. A specific form of CSA is the so-called periodic or Cheyne-Stokes respiration (CSR), with breathing "spindles" (gradually increasing and decreasing breathing amplitudes) between apneas. CSA and CSR are characteristic in hypertension only if congestive heart failure or cerebral lesions (e.g., post-stroke status), the main determinants of the appearance of CSA, are present as associated conditions. Mixed (obstructive + central) SA could also occur in patients with hypertension [2, 3].

Because of its high prevalence and clinical importance in hypertension, in the following, mainly data related to OSA will be presented.

3. Epidemiological data and evidences regarding the close relationship between OSA and hypertension

The prevalence of OSA (AHI ≥ 5 and the presence of at least one symptom induced by altered sleep) in the general population is high, especially because of the increasing occurrence of obesity. Roughly, 20–30% of men and 10–15% of women suffers from OSA. Significant OSA (moderate or severe, with AHI ≥ 15) is present in about 15% of males and 5% of females. However, there is a concern regarding underestimation of the real prevalence of OSA especially in women, who frequently have atypical symptoms. The prevalence increases with advancing age, race, ethnicity (African Americans and Hispanics) and body mass index [7, 8].

There exists a large amount of epidemiological data and evidences regarding the bidirectional, complex relationship between OSA and hypertension. The prevalence of OSA in hypertensive patients is about 30–50%, while hypertension is present in OSA patients in about 50%. The relationship between the prevalence/severity of OSA and the grade of hypertension is almost linear. The best example for this fact serves the case of resistant hypertension, when the prevalence of any OSA is about 80%, while the presence of moderate or severe OSA reaches 56% [2, 9–11]. Relative to other hypertensive patients, the risk of OSA is 2.5-fold increased in patients with resistant hypertension, and, in the same time, OSA is more severe in patients with resistant hypertension than in those without [12].

Despite of the existence of potential confounders, like obesity, age, sex, metabolic syndrome, and diabetes mellitus, epidemiological data clearly demonstrate the independent association between OSA and incident and prevalent hypertension [13–15].

4. Risk factors of OSA, clinical manifestations, and nocturnal clinical events

Epidemiological data consistently support the existence of risk factors of developing and progression of OSA. These risk factors contribute to the anatomical and/or functional narrowing of the upper airways (e.g., fat deposition in the surrounding tissues in obesity), enhancing their susceptibility to collapse [16].

The principal risk factors of OSA are age, male gender, obesity, and abnormalities of the upper airways and craniofacial structures (especially in Asian subjects) [17]. Obesity and overweight could be considered the most important risk factors due to their high prevalence both in patient with OSA and hypertension. Also, the increasing tendency of obesity in the general population could be considered as the main responsible for the continuously increasing prevalence of both OSA and hypertension. A 10% increase in body mass is associated with a sixfold increase in risk of incident OSA, and, in a population-based study, moderate to severe OSA (AHI ≥15) was present in 63%/22% (male/female) of patients with BMI ≥30 kg/m^2 [17–21].

Other important risk factors of OSA include smoking, alcohol use, sedative or narcotic intake before sleep, nasal obstruction, menopause, and family history (for snoring or OSA).

Nocturnal symptoms	Diurnal symptoms
Heavy, loud snoring	Feeling of an inadequate, unrestful sleep
Restless, interrupted sleep	Excessive sleepiness with/without episodes of involuntary
Awakenings with choking, gasping	Tiredness, falling asleep (e.g., causing car accidents)
Insomnia	Attention, memory, and cognition deficits
Observed apneas by sleep partner	Decreased performance at school, workplace, etc.
Nocturia	Mood disorders: depression, anxiety
Sweating	Sexual dysfunction: loss of libido, impotence
Dry mouth	
Acid reflux	
Morning headache and dizziness	
Nocturnal clinical events	
Myocardial ischemia—silent, angina, myocardial infarction	
Arrhythmias—bradycardias, supraventricular arrhythmias, atrial fibrillation, ventricular arrhythmias, sudden cardiac death	
Blood pressure ascensions	
Acute cardiac decompensation (left and/or right heart failure)	
Stroke (ischemic, hemorrhagic)	

Table 1. Nocturnal and diurnal symptoms and nocturnal clinical events related to OSA [2, 22, 23].

The prevalence of OSA was found to be increased in association with some medical conditions, such as pregnancy, congestive heart failure, chronic pulmonary disease (asthma, chronic obstructive pulmonary disease, pulmonary fibrosis), end-stage kidney disease, stroke, and endocrine disorders (hypothyroidism, acromegaly, polycystic ovary syndrome) [16, 17, 22].

The main clinical manifestations of OSA are presented in **Table 1**. Diurnal symptoms are the consequences of the insufficient, fragmented, low-quality sleep caused by multiple arousals induced by apnea. The complex pathophysiology of the nocturnal clinical events will be presented in detail later.

5. Pathophysiological basis of sleep apnea-hypertension relationship

The complex pathophysiological mechanisms behind acute clinical events and chronic medical conditions, including hypertension, induced and/or aggravated by OSA, are presented in **Table 2**.

The most important mechanisms related to OSA that play a role in the genesis and progression of hypertension are the long-term activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. Also, during arousals, the acute sympathetic

Pathophysiological mechanism	Consequences
Hypoxemia Hypercapnia Repetitive hypoxia-normoxia cycles (also present in CSA)	**1.** Ischemia (myocardial, cerebral, etc.) **2.** Bradycardia (during apnea)—tachycardia (caused by arousal) **3.** Oxidative stress and systemic inflammatory reaction • Endothelial dysfunction—accelerated atherosclerosis **4.** Hypoxic pulmonary vasoconstriction • Acute and chronic increase of pulmonary arterial pressure with right ventricular overload **5.** Decreased baroreflex activity—contributing to hypertension **6.** Activation of the sympathetic nervous system due to increased chemoreflex sensitivity • Hypertension (acute and chronic) • Sinus tachycardia • Arrhythmias • Ischemia (increased oxygen demand) • Cardiac toxicity and remodeling (e.g., hypertrophy) • Endothelial dysfunction—accelerated atherosclerosis • Insulin resistance, metabolic syndrome **7.** Activation of the renin-angiotensin-aldosterone system
Arousals (with or without awakenings) (also present in CSA)	**1.** Acute activation of the sympathetic nervous system and withdrawal of the parasympathetic cardiac control
Negative intrathoracic pressure during inspiratory effort (only in OSA)	**1.** Increased transmural pressure of cardiac cavities, great vessels, and pulmonary arterial bed • Increased left and right ventricular afterload ○ Acute and chronic cardiac decompensation ○ Ischemia (increased oxygen demand) ○ Arrhythmias • Atrial dilation—favoring atrial fibrillation • Aortic dilation • Pulmonary fluid retention, contributing to acute cardiac decompensations

Table 2. Pathophysiological mechanisms and their consequences in the setting of OSA [2, 23, 24].

hyperactivation causes blood pressure increases, which could precipitate acute cardiac decompensation, myocardial ischemia, arrhythmias, or stroke.

The characteristics of hypertension in the case of significant OSA as comorbidity are the high blood pressure values during nighttime (nocturnal blood pressure surge) and the concomitant non-dipping behavior of 24-hour values. Also, blood pressure variability is increased and heart rate variability is blunted, as markers of cardiac autonomic dysfunction. The control of blood pressure values could be difficult in many cases, development of resistant hypertension with target organ damage (e.g., left ventricular hypertrophy) being the rule [25, 26].

Masked hypertension was also found to be more prevalent in patients with OSA; in one study 30% of newly diagnosed OSA patients had masked hypertension [27].

In patients with hyperaldosteronism, there is a higher prevalence of OSA (1.8 times). Fluid retention induced by aldosterone and its redistribution to the neck tissues is a major contributor to this finding. This mechanism (a vicious circle) contributes significantly to the higher prevalence of coexisting resistant hypertension and severe OSA in these patients [28].

Experimental and human studies data support that the relationship between hypertension and OSA is bilateral. Blood pressure increases, by baroreceptor activation, could inhibit the upper airways muscle tone, enhancing their tendency to collapse [29].

6. Diagnosis of SA in clinical practice

The diagnosis of SA in hypertensive patients does not differ from those without hypertension. The diagnostic approach has two main elements: screening and confirmation (definitive diagnosis).

First, screening is mandatory when significant nocturnal and/or diurnal symptoms are present in a patient. These could be observed or find out by the patient itself, by his/her bed partner, or by different surrounding persons (including the medical personnel). The most important symptoms in this regard are heavy snoring, restless sleep, awakenings associated with choking, witnessed apnea, and excessive daytime sleepiness. Also, screening is recommended if pronounced risk factors or certain clinical conditions are present: severe obesity, hardly controllable, resistant hypertension (usually with target organ damage and non-dipping 24-hour pattern), frequent nocturnal palpitations or proven nighttime arrhythmias, atrial fibrillation recurrence(s) after cardioversion(s), therapy refractory heart failure or frequent decompensations, “unexplained” pulmonary hypertension and right ventricular overload, and nocturnal stroke without an overt etiology [2, 5].

The most used screening tools are the comprehensive sleep evaluation, the sleep apnea questionnaires, and the overnight pulse oximetry. The latter method consists of a demonstration of oxygen desaturations (an indirect measure of SA) during the night. It cannot differentiate the obstructive and central apneas.

There are multiple validated (against PSG and HSAT) sleep questionnaires, morphometric and clinical prediction models which are based on the testing of the presence of the most

important symptoms and features related to SA/OSA. The most used are the Epworth's, Berlin, and STOP-BANG questionnaires. The Epworth Sleepiness Scale (moderate sensitivity, good specificity) involves eight questions to assess excessive daytime sleepiness [5, 30, 31]. The Berlin questionnaire (good sensitivity, moderate specificity) uses eleven questions (from three categories) to determine the risk of patient for OSA [5, 31, 32]. The STOP-BANG questionnaire (high sensitivity and good specificity) is a more and more popular tool for OSA screening and is based on four yes/no questions and on four clinical features (**Table 3**) [5, 31, 33, 34]. Current guidelines recommend against using any screening tool to diagnose OSA in adults, in the absence of PSG or HSAT [5].

The definitive diagnosis of SA is always device-based. Every patient with high clinical suspicion of SA, based on a comprehensive sleep evaluation, screening tools, and/or the presence of the cardinal symptoms of OSA (excessive daytime sleepiness and at least two of the following: loud snoring, witnessed apnea or gasping or choking, diagnosed hypertension), has to undergo overnight sleep monitoring [5].

1. Snoring?	**Yes/No**
Do you snore loudly (loud enough to be heard through closed doors or your bed partner elbows you for snoring at night)?	
2. Tired?	
Do you often feel tired, fatigued, or sleepy during the daytime (such as falling asleep during driving or talking to someone)?	
3. Observed?	
Has anyone observed you stop breathing or choking/gasping during your sleep	
4. Pressure?	
Do you have or are being treated for high blood pressure?	
5. Body mass index more than 35 kg/m^2?	**Yes/No**
6. Age older than 50?	
7. Neck size large? (measured around Adam's apple)	
For male, is your shirt collar 17 inches/43 cm or larger?	
For female, is your shirt collar 16 inches/41 cm or larger?	
8. Gender = Male?	
OSA—Low risk: Yes to 0–2 questions	
OSA—Intermediate risk: Yes to 3–4 questions	
OSA—High risk: Yes to 5–8 questions	
or Yes to 2 or more of 4 STOP questions + male gender	
or Yes to 2 or more of 4 STOP questions + BMI > 35 kg/m^2	
or Yes to 2 or more of 4 STOP questions + neck circumference 17 inches/43 cm in male or 16 inches/41 cm in female	

Table 3. The STOP-BANG questionnaire and its evaluation.

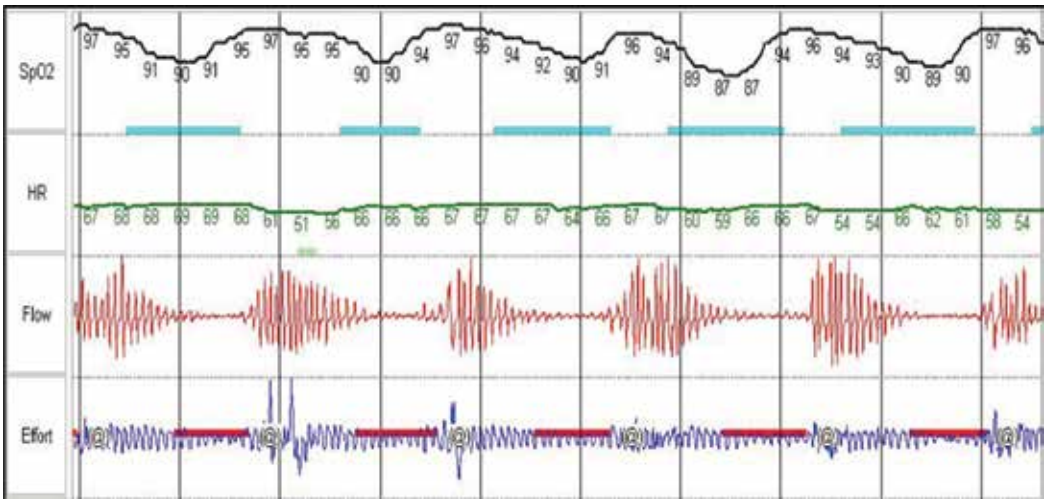

Figure 1. A typical registration with a Type III sleep monitor from a patient with OSA. SpO2—oxygen saturation, HR—heart rate, flow—nasal airflow, effort—chest movements (maintained during apneas).

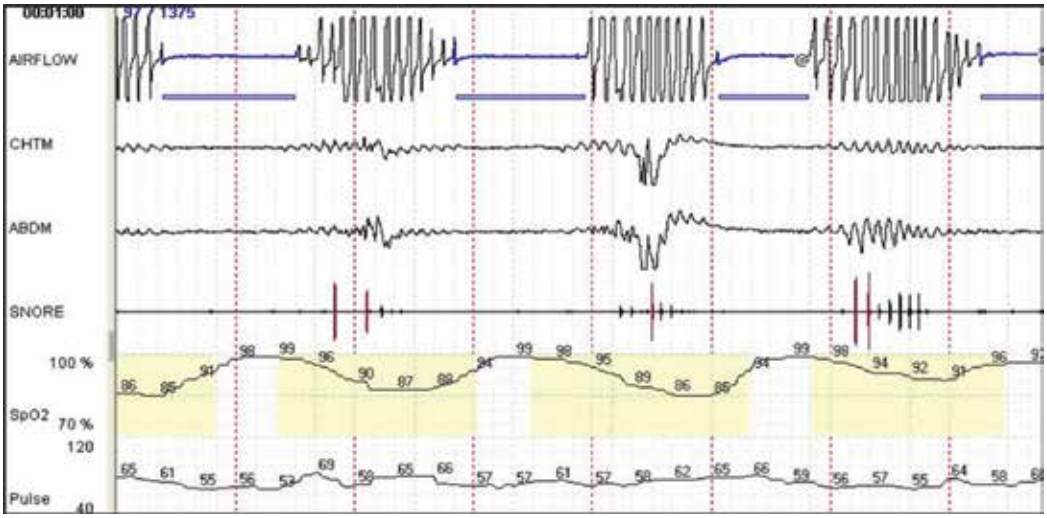

Figure 2. A typical registration with a Type III sleep monitor from a patient with CSA. Airflow—nasal airflow; CHTM, ABDM—chest and abdominal movements (absents during apneas); SNORE—snoring; SpO2—oxygen saturation; pulse—heart rate.

The diagnostic devices are categorized as Type I to IV depending on the number of biological signals (channels) monitored. PSG represents the gold standard of sleep monitoring, having the capability to register the following channels: EEG, EOG, ECG/heart rate, chin EMG, limb EMG, respiratory effort at thorax and abdomen, airflow from a nasal cannula, pulse oximetry, etc. (a minimum of 7 channels). PSG could be used for Type 1 (attended, in the sleep laboratory) and Type 2 (unattended, at home) sleep studies. In the case of HSAT, as a rule, Type III

	Recommendation statement	Strength of recommendation
1.	We recommend that clinical tools, questionnaires, or prediction algorithms not be used to diagnose OSA in adults, in the absence of PSG or HSAT	Strong
2.	We recommend that PSG, or HSAT with a technically adequate device, be used for the diagnosis of OSA in uncomplicated adult patients presenting with signs and symptoms that indicate an increased risk of moderate to severe OSA	Strong
3	We recommend that if a single HSAT is negative, inconclusive or technically inadequate, PSG be performed for the diagnosis of OSA	Strong
4.	We recommend that PSG, rather than HSAT, be used for the diagnosis of OSA in patients with significant cardiorespiratory disease, potential respiratory muscle weakness due to neuromuscular condition, awake hypoventilation or suspicion of sleep-related hypoventilation, chronic opioid medication use, history of stroke, or severe insomnia	Strong
5.	We suggest that, if clinically appropriate, a split-night diagnostic protocol, rather than a full-night diagnostic protocol for PSG, be used for the diagnosis of OSA	Weak
6.	We suggest that when the initial PSG is negative, and there is still clinical suspicion for OSA, a second PSG be considered for the diagnosis of OSA	Weak

Table 4. Current recommendations of the AASM regarding the use of PSG and HSAT for diagnosing OSA [5].

devices with minimum 4 channels (airflow, respiratory movements, pulse oximetry—heart rate; optionally: ECG, body position, snoring, etc.) are used. In **Figures 1** and **2** typical recordings, using a Type III device, are presented from a patient with severe OSA and from another with severe CSA. The portable, Type III devices used for HSAT have the disadvantage vs. PSG, that they do not monitor the sleep itself (lack of EEG, EOG, EMG) and do not provide real-time data with the possibility of on-line corrections of monitoring. Due to these facts, and to the relatively frequent measurement artifacts, patients with equivocal sleep monitoring results have to undergo a standard, attended PSG in the sleep laboratory [5, 6, 35].

Current recommendations of the AASM regarding the diagnostic use of PSG and HSAT are presented in **Table 4**.

7. The effect of OSA interventions on comorbid hypertension

Complex treatment of moderate/severe OSA is mandatory in the setting of hypertension, the expected results being a better quality of life of the patients and a more efficient blood pressure control.

The control of modifiable factors which contribute to both conditions—reducing obesity, smoking, and alcohol consumption—is considered a very effective, first step treatment modality of comorbid OSA and hypertension [23, 24, 36].

The standard and efficient device-based therapy of OSA consists of the utilization of continuous positive airway pressure (CPAP). In the literature, there are a plenty of studies, usually

sham-CPAP controlled, concerning the impact of CPAP treatment on comorbid hypertension with diverse grades. The results of these studies, sometimes contradictory, are presented and commented in detail in recent meta-analyses and critical reviews [37, 38, 39]. The effects of CPAP treatment on blood pressure (hypertension) in OSA patients could be summarized as follows: (1) prehypertension and masked hypertension are reduced [40], (2) there is a clear tendency of decreasing both the nighttime and daytime blood pressure values (but only modest reductions, generally 2–5 mmHg), (3) there is a slight reversal of the non-dipping behavior, and (4) the effect of CPAP treatment seems to be more pronounced if there is a good treatment adherence (use of the device at least 5 hours/night), the patient is more symptomatic, and the OSA and/or hypertension are more severe [37, 38, 39]. As a conclusion, CPAP treatment in comorbid OSA and hypertension is a relatively modest, but efficient, additive modality of controlling blood pressure values. The beneficial effects of CPAP treatment are the results of reducing sympathetic overactivity by controlling hypoxemia, arousals, and negative intrathoracic pressure.

Oral appliance therapy, a treatment option in mild and moderate forms of OSA, also could improve blood pressure control in the case of concomitant hypertension [41, 42].

Regarding the effect of antihypertensive drugs on OSA in hypertensive patients, the (sometimes conflicting) data do not support clearly a specific beneficial effect of the usually prescribed drugs (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, beta-blockers) [23, 24]. However, hypertensive patients with hyperaldosteronism and those with resistant hypertension could benefit from spironolactone as first choice therapy, with proven beneficial effects on OSA. Generally, diuretics by reducing fluid retention, including that at the level of parapharyngeal tissues, could ameliorate upper airway obstruction and OSA [43, 44].

8. Conclusion

Hypertension and SA, especially OSA, are frequently associated, and there is a well-documented pathophysiological link between OSA and development and aggravation of hypertension. Screening and diagnosis of OSA is mandatory whenever increased nocturnal and daytime symptoms and/or difficult to control hypertension (resistant, as a rule, with high nocturnal blood pressure values and target organ damages) is present. The treatment of OSA by specific (e.g., CPAP) or nonspecific means could contribute significantly to a better quality of life of the patients, to a better control of blood pressure values, and to the decrease of OSA-related adverse clinical events.

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Conflicts of interest

The authors declare that there are no conflicts of interest regarding the writing of this chapter.

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Chapter 5

Non-Dipping Patten of Blood Pressure and Gestational Hypertension

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Abstract

Gestational hypertension (GH) is one of the entities of the hypertensive disorders in pregnancy (HDP), a major cause of maternal, fetal, and neonatal morbidity and mortality. Also, the HDP have been recognized as an important risk factor for cardiovascular diseases. Thus, women who develop GH or preeclampsia (PE) are at increased risk of hypertension, ischemic heart disease and stroke in later life. An ambulatory blood pressure monitoring (ABPM) takes an important role in diagnosing of hypertension in pregnancy. Also, it has been shown that ABPM had higher accuracy in the prediction of GH, premature childbirth and low birth weight, compared with the conventional blood pressure (BP) measurements. In addition, we have found that non-dipping pattern of BP is very highly related with worse pregnancy outcome in a term of preterm delivery and intrauterine growth restriction. Also, it is associated with worse maternal hemodynamics, more impaired systolic function and more pronounced cardiac remodeling compared to women with GH and dipping pattern of BP. This review aimed to explore the (a) current classifications of the HDP; (b) pathogenesis of GH and PE; (c) physiological changes of BP and maternal hemodynamics in pregnancy; and (d) pathophysiological changes of BP and maternal cardiac function, especially in a term on BP pattern.

Keywords: echocardiography, fetal growth restriction, hemodynamics, pregnancy, blood pressure, cardiac function

1. Introduction

The hypertensive disoders in pregnancy (HDP) have a great clinical significance both for mother and for fetus, complicating up to 15% of pregnancies. Approximately 15–33% of the total maternal mortality and quarter of all antenatal admissions during pregnancy is due to HDP [1]. Hypertensive pregnant women are at higher risk of intracranial bleeding, severe organ failure and disseminated intravascular coagulopathy. Hypertension is associated with placental abruption, intrauterine growth restriction (IUGR) and fetal death. Fetal mortality is 4% higher if mother has hypertension during pregnancy, and even 7% more if preeclampsia (PE) develops [2–4]. In addition, preeclampsia is one of the most common causes of preterm delivery and 25% cases of very low birth weight (<1500 g) is due to PE. Also, it has been found that mothers' deaths due to HDP in developing countries, are taking epidemic proportions, and that mortality rates in these countries are 100–200 times higher than in Europe and North America [5].

2. Hypertensive disoders in pregnancy, definition and classification

2.1. Definition of hypertension in pregnancy

The definition of hypertension in pregnancy is based on absolute blood pressure (BP) values according to the JNC 8 classification and is defined as systolic blood pressure (SBP) value ≥140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg [1, 6]. In contrast to the gradation of hypertension of the European Association for Hypertension for a general (non-pregnant) population there are two stages of hypertension in the pregnancy: mild (140–159/90–109 mmHg) and severe (≥160/110 mmHg) hypertension [7, 8].

2.2. Classification of hypertensive disoders in pregnancy

There are several classifications of the hypertensive disoders in pregnancy (HDP) in contemporary literature.

We consider that the classification of the International Society for the Study of Hypertension in Pregnancy (ISSHP) is the most appropriate and least confusing: chronic hypertension, gestational hypertension (GH), preeclampsia (PE)—de novo or superimposed on chronic hypertension and white coat hypertension (WCH) [9].

2.2.1. Chronic hypertension

Chronic hypertension exists before pregnancy or develops before 20 weeks of gestation (GW) and persists 42 days post-partum. It complicates 1–5% of pregnancies and may be associated with proteinuria.

2.2.2. Gestational hypertension

Gestational hypertension (GH) is pregnancy-induced hypertension with occurrence after 20 GW and resolves within 42 days post-partum. This means that after 42 days post-partum, re-assessment to be sure that it is not chronic hypertension, is necessary. It is characterized by poor organ perfusion. It complicates 6–7% of pregnancies. [8].

2.2.3. Preeclampsia: de novo or superimposed on chronic hypertension

If GH is associated with clinically significant proteinuria (≥0.3 g/day in a 24 h urine collection) then it is known as preeclampsia (PE). It is a pregnancy-specific syndrome that occurs after mid-gestation, defined by de novo appearance of hypertension, accompanied by new-onset of significant proteinuria. It is a systemic disorder with both maternal and fetal manifestations. Edema is no longer considered part of the diagnostic criteria, as it occurs in up to 60% of normal pregnancies. Overall, PE complicates 5–7% of pregnancies, but increases to 25% in women with chronic hypertension. It is associated with placental insufficiency, often resulting in IUGR [8, 10]. ISSHP consider that PE is diagnosed when de novo hypertension is accompanied by (a) proteinuria, or (b) evidence of other maternal organ system dysfunction such as impaired GFR, neurological problems, thrombocytopenia, abnormal liver function or (c) fetal growth restriction. Severe PE includes blood pressure ≥ 160 mmHg systolic or ≥110 mmHg diastolic but is not based upon the degree of proteinuria. This is recommended for use in research but in clinical practice all cases of preeclampsia should be considered potentially severe. Early onset preeclampsia is apparent before 34 GW. It is important to note that PE occurs in about 50% of pregnant women in whom GH appeared between 24 and 35 GW [8].

Symptoms and signs of severe preeclampsia include (**Figure 1**): pain in the upper abdomen (due to liver edema/hepatic hemorrhage), headache—visual disturbance (cerebral edema), hyperreflexia—clonus—convulsions (cerebral edema), HELLP syndrome: hemolysis, elevated liver enzymes, low platelet count.

Since proteinuria may appear later, pregnant woman with de novo hypertension accompanied by headache, visual disturbances, abdominal pain, or abnormal laboratory tests, specifically low platelet count and abnormal liver enzymes should be treated as PE [9, 11].

The relatively new term is non-proteinuric PE. Recent study highlighted differences between non-proteinuric PE and GH and suggested that the subclassification of "non-proteinuric preeclampsia" should be added to existing classification of HDP. It is worth mentioning that non-proteinuric PE presents significant risk to the mother but less risk to the baby than proteinuric PE [12]. ISSHP recommends a diagnosis of preeclampsia that may not necessarily include proteinuria [9].

2.2.4. White-coat hypertension

White-coat hypertension (WCH) has been recognized in one quarter of patients with elevated office blood pressure (OBP) in the general population [13]. If a diagnosis of WCH is confirmed in the first half of pregnancy, that means normal BP using 24 h ambulatory BP monitoring (ABPM), pregnant women can be managed with regular home blood pressure (HBP)

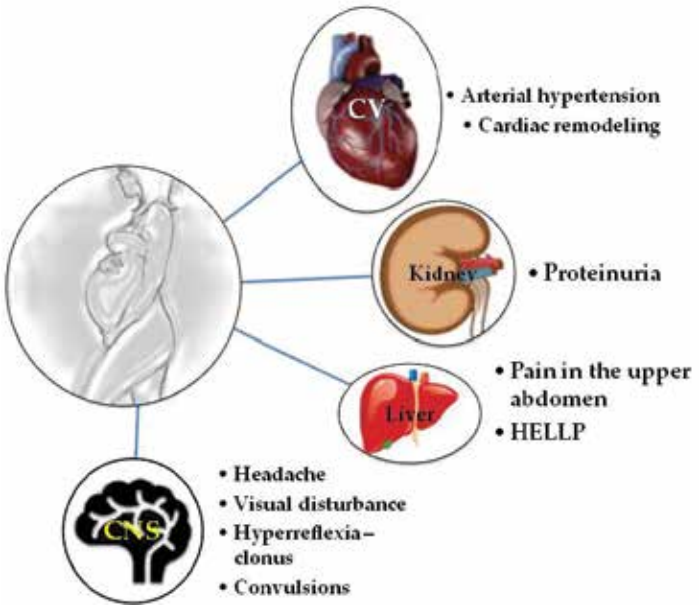

Figure 1. Signs and symptoms of severe preeclampsia (HELLP: hemolysis, elevated liver enzymes, low platelet count).

assessments. Antihypertensives can be avoided, at least up to BP levels of 160–170/110 mmHg. It is considered that near half women with WCH will develop true GH or PE [14].

ISSHP recommends that the criterion for defining hypertension in pregnancy depends on the method of measuring BP. If OBP measurement is ≥140/90 mmHg before 20 GW, it is necessary to preform ABPM. If values are:

- awake BP ≥ 130 /80 mmHg
- sleep BP ≥ 115/70 mmHg,

it is a diagnose of chronic hypertension and risk of PE is 25%. There is a need to monitor with HBP measurement if a white-coat effect is apparent on ABPM.

If values are:

- awake BP ≤ 130 /80 mmHg
- sleep BP ≤ 115/70 mmHg,

it is a diagnose of WCH, risk of GH is 50% and risk of PE is 8%.

For HBP measurement ≥135 /85 mmHg after 20 GW, hypertension is diagnosed [15].

3. Pathogenesis in gestational hypertension and preeclampsia

It is still common to consider GH and PE as "diseases of many theories" [16].

The most consistent findings indicate that an inadequate function of trophoblast, plays an important role in their origin. Actually, in normotensive pregnancies trophoblasts invade the wall of the spiral arteries and this process takes place in two phases. The first one is during the first trimester when there is a significant transformation of the decidual parts of the spiral arteries. There is a degeneration of an inner, elastic layer, and consequently the destruction of a middle, muscular, and external layer. Destroyed structures of the arterial wall are replaced by hyaline and fibrin.

The second phase coincides with the second trimester. At that time, the endovascular invasion of trophoblast involves the segment of the arcuate arteries, belonging to the myometrium. Unlike the first phase, the invasion takes place only to the muscular layer. Process is the most intense between 16 and 20 GW, and at the same time there is the largest drop in resistance of uteroplacental circulation. These morphological changes allow maximum blood flow with the least resistance through dilated blood vessels to the fetus. On the other hand, morphologically altered blood vessels become relatively insensitive to vasoconstrictor substances because they have very few smooth muscles.

The lack of endothelin 1 (ET1) in trophoblast cells during the first trimester causes inadequate proliferation and invasion of trophoblast cells, causing the absence of physiological changes in the spiral arteries of the uterus, the musculoelastic layer of spiral arteries remains unchanged, and the arteries remain narrowed throughout the pregnancy and sensitive to vasoconstrictor substances. As a consequence, there is a reduced blood supply of the placenta and hypoxia of the placenta and the fetus. This causes increased secretion of ET1 with an increase in its concentration in the bloodstream and consequent vasoconstriction. The pathophysiological mechanism itself further leads to so-called "vicious cycle" (**Figure 2**) because vasoconstriction provokes insufficiency of the placenta. This is an oxidative stress that causes an endothelial dysfunction, leads to reduced secretion of vasodilatory substances (nitric oxide—NO, prostacyclin, thromboxane A2), with simultaneous increased secretion of vasoconstrictor substances (ET1, serotonin, neuropeptide Y). Another, not less important reason for provocation and

Figure 2. Pathophysiology of gestational hypertension and preeclampsia—"vicious cycle".

maintenance GH, is an increased reactivity of blood vessels to angiotensin II in women with this type of hypertension (in normotensive pregnant women, reactivity to this most powerful vasoconstrictor is physiologically reduced) [16–20].

4. Physiology changes in arterial blood pressure in pregnancy

There are numerous changes in the body of the pregnant woman as a result on an adaptation to the newborn condition. In the first trimester of pregnancy, due to a development of a new vascular network, relaxation of the blood vessels and increased influence of mediators such as NO, prostacyclin, thromboxane A2, peripheral vascular resistance decreases, causing a systemic vasodilatation which results in a physiological fall in arterial BP in that period. Systolic BP drops during the first two trimesters, with an increase in the third. Due to declining tonus of blood vessels, the decrease of diastolic BP is more prominent than systolic.

This may mask the chronic hypertension and, when hypertension is recorded later in pregnancy, it may be interpreted as gestational.

Although there is an increase in plasma renin activity during pregnancy, blood vessels of pregnant women are refractory to the vasoconstrictor effect of angiotensin II. In the further course of gravidity, there is an increase of BP, but always in the reference values [21–25]. Mean arterial pressure (MAP), as well as peripheral vascular resistance, are also decreased during the first two trimesters, and elevated in the third trimester [26].

5. Changes of blood pressure in gestational hypertension

As it has been already mentioned, in contrast to normotensive pregnancy characterized by systemic vasodilatation, there is systemic vasoconstriction that caused the increase in the total vascular resistance (TVR) in GH [27, 28]. More frequent absence of dipping profile of BP in women who develop hypertension in pregnancy was registered by performing ABPM [29–31].

5.1. 24-h arterial blood pressure pattern

5.1.1. Classification

There is a predictable pattern of BP in healthy individuals—BP is normally lower during the night-time and higher during the daytime. A dipping pattern represents a drop of nocturnal BP for >10%, of the daytime BP—their ratio is between 0.8 and 0.9 [32]. Absence of the night-time BP drop (<10% of the daytime BP, i.e., their ratio is between 0.9 and 1—non-dipping pattern) is a crucial risk factor for the cardiac and cerebrovascular events, also for the remodeling of the left ventricle (LV) in general population [33]. An increase in the prevalence of dipping profile by 10% reduces cardiovascular morbidity for 25% [34].

It is necessary to know that there are so-called extreme dippers—when a nocturnal drop of BP is >20%, (average nightly and average daily BP ratio is less than 0.8) and inverse dippers—there is no drop in BP during the night, on the contrary, there is an increase over the daily BP values (the ratio of average nightly and average daily BP is greater than 1) [32, 35].

5.1.2. The causes of the non-dipping pattern of blood pressure

There are several causes of the non-dipping pattern of BP: endocrinological disorders, renal dysfunction, disorder of the autonomic nervous system, salt-sensitivity hypertension, preeclampsia, malignant hypertension, heart transplantation, menopause, ethnicity, sex, metabolic syndrome, obesity, age, and smoking.

Some of the listed reasons can be of importance for developing GH.

5.1.2.1. Disorder of the autonomic nervous system

It is known that excessive sympathetic activity or decreased parasympathetic activity has an inadequate drop in BP during the night [36]. There is the greatest sympathetic activity overnight in inverse dippers [37], i.e., there is a significant negative correlation between sympathetic activity and a fall of BP during the night. Non-dippers have a lower drop in catecholamine levels in the urine overnight compared with dippers, and a higher activity of an α1-adrenergic receptors. [38].

5.1.2.2. Sensitivity to NaCl

Hypertensive patients, sensitive to NaCl intake do not have an adequate fall in night-time BP, while they are eating a food rich in salt. If they reduce the NaCl intake, they become dippers. The opposite, people who are resistant to NaCl intake, has no significant change in BP overnight regardless of salt intake [39, 40].

5.1.2.3. Obesity

The body mass index is inversely proportional to the drop in the night-time BP, and the prevalence of the non-dipping pattern is greater among obese people [41]. The possible cause is an increase in the concentration of catecholamines in the blood of obese people [42].

5.1.2.4. Gender

Hypertensive women with non-dipping profile have a significantly higher risk of cardiovascular events in the future than women with dipping pattern. There is no such difference in men [43].

5.1.2.5. Preeclampsia

It has been shown that there is a connection between non-dipping profile in the first trimester of pregnancy in normotensive pregnant women with a subsequent onset of hypertension and PE, but also with IUGR [44, 45]. Eight of hypertensive pregnant women whose pregnancy were complicated with PE, had an increased activity of the sympathetic autonomic nervous system [46].

5.2. Role of 24-h ambulatory blood pressure monitoring

ABPM provides the most accurate and reliable determination of the BP pattern. The results obtained by ABPM significantly more correlated with target organ damage, as well as with the prognosis of cardiovascular events, than the results obtained during an OBP measurements [33, 47–50]. In addition, ABPM is also recommended for the detection of the WCH [13].

It has been shown that ABPM is superior to OBP in the prognosis of premature termination of pregnancy, low birth weight and onset of proteinuria later in pregnancy [51–53]. A prospective double-blind study, revealed that differences in the daily-night BP pattern in hypertensive pregnant women can be helpful in determining the severity of PE and that the increase in night-time BP predominantly occurs in PE [54].

It is well known that nocturnal hypertension is associated with an exacerbation of endothelial damage in PE [55]. On the other hand, recent study has shown that the non-dipping pattern of BP in GH is associated with IUGR, preterm delivery and with the deterioration of maternal hemodynamics [56].

6. Physiology changes in cardiac function and geometry in pregnancy

Due to so-called systemic vasodilatation, characteristic of the first and the second trimester of pregnancy and decreased resistance of peripheral arteries, activation of the compensatory homeostatic mechanisms of blood flow—sympathetic nervous system, renin-angiotensin-aldosterone system, and non-osmotic secretion of vasopressin occurs. It leads to retention of sodium and water, and consequently to a purposefully increase of intravascular fluid to provide sufficient uteroplacental circulation in order to assure development and growth of the fetus [57]. This expansion of the intravascular volume leads to an increase in stroke volume (SV), which reaches the highest values between 30 and 36 GW. Due to this increase, but also because of the rise in heart rate, the cardiac output also (CO) increases. Compared with the period before pregnancy, the heart rate is 16–35% higher during pregnancy [58–61], as a compensatory mechanism due to vasorelaxation, to provide an adequate CO [23].

All mentioned leads to changes in cardiac morphology and systolic and diastolic function during pregnancy. Myocardial contractility increases, resulting in a shortening of the pre-ejection time with the prolongation of the left ventricular (LV) ejection time (ET), which is consequence of an increased SV. Most studies have shown that the parameters of systolic function, such as an ejection fraction (EF), end-diastolic volume of the LV (LVEDV), SV, ET, the systolic velocity of the mitral-septal and lateral anulus (s'), progressively increase during pregnancy, with a slightly lower value in the third trimester [62–64]. There is an increase in the volume of the left and right atrium, the left and right chambers, and the thickening of the walls of the LV, which with an increased preload in the first half of the pregnancy and an increased afterload in the last trimester of pregnancy, leads to physiological cardiac hypertrophy and to increase of myocardial mass. The LV hypertrophy becomes visible in the second trimester, while maximum values are reached toward the end of the pregnancy [23, 25, 61, 62, 64]. Myocardial mass is 12–30% higher than before pregnancy [23, 25, 61]. Due to increased preload, and therefore increased LVEDV, according to Frank Starling's law, there is an increase

in the strength of muscle contraction during the systole. Also, due to the increase in LVEDV and end-diastolic left ventricular diameter, there is an increase of the pressure on the walls of the LV, that leads to increased CO and oxygen demands. According to Laplace's law, wall stress is directly proportional to the pressure on the wall of the LV and the radius of the chamber, and inversely proportional to the thickness of the walls. In order to reduce wall stress, the walls of the left ventricle become thicker [65–67].

An increased preload in the first and the second trimester of pregnancy also affects changes in diastolic function, and there is an increase of the velocity of an early filling of the LV (E), but also an increase of the velocity of a late filling of the LV (A). Thus, during this period, the ratio E/A remains unchanged. In the last trimester of pregnancy, when there is an increase of MAP and peripheral vascular resistance, and consequently increase of afterload, the early stage of diastolic filling slows down. It is reflected in the reduction of E wave velocity and the deceleration time of E wave (DTE). As a consequence, there is a greater retention of blood in the left atrium (LA) at the end of the diastole, and consequently increase of LA work that leads to an increase of A wave velocity. The increase of A wave is also affected by an increase of heart rate. During this period there is a decrease of E/A ratio [63–69]. While some authors suggested that there is prolongation of the isovolumetric relaxation time of the LV (IVRT), others did not show significant changes in it during pregnancy [70].

7. Changes in cardiac function in gestational hypertension/preeclampsia

There are two hemodynamic disorders, characteristic for GH and PE, both the consequences of the endothelial dysfunction: reduction of CO and increasing of TVR. The first one is a result of the reduction of the total plasma volume [71–73]. The second one occurs because of vasoconstriction, increased sensitivity of blood vessels to angiotensin II and increased peripheral vascular resistance. It is interesting to note that the transition from a hypervolume state with increased CO and decreased TVR into a condition characterized by low CO and high TVR coincides with the clinical manifestation of symptoms and signs in women whose pregnancies are complicated by hypertension and preeclampsia [26, 28, 74, 75].

7.1. Systolic function in gestational hypertension/preeclampsia

Mentioned hemodynamic changes affect the function and morphology of the LV. According to the literature data, which are unfortunately, due to the specificity of the problem, still scarce and done in a small number of cases, there is mainly a change of the diastolic function of LV in GH, while the data on the change of the systolic function are fewer and more controversial [76–79].

The systolic function is determined by the ability of the heart muscle to make contraction and to pump the blood (stroke volume) into the arterial system. One of the reasons for an inconsistent data about systolic function of the LV in GH is that in most studies the systolic function was evaluated using standard parameters such as EF and SV, which are dependent, besides the contractility of the heart, on volume and heart rate. Besides, the heart loses its classical ellipsoid shape during the pregnancy [23, 80]. In order to avoid the influence of geometric remodeling, but also the influence of preload, the longitudinal systolic function of the LV has

to be evaluated (**Figure 3**). Myofibrils of the LV are arranged mainly longitudinally and oblique in the subendocardial and subepicardial layers, and circumferently in the middle layers. LV subendocardial fibers are more susceptible than the circumferential fibers to the effects of ischemia or pressure-load. First, there is a contraction of the longitudinal and the oblique myofibrils at the onset of the systole, causing a spherical LV shape, and then contraction of the circumferential myofibrils, which are responsible for the ejection [81].

The longitudinal systolic velocity—s′ and end-systolic elasticity of the left ventricle (Ees), parameters independent of the volume, are more precise measure of contractility of the heart than EF and SV [64, 82–86]. More recently, the relationship between effective arterial elasticity (Ea), which is the measure of afterload, and the elasticity of the LV at the end of the systole—Ea/Ees, has been used. The elasticity of the LV at the end of the systole shows how much the end-systolic volume of the LV increases, and the SV decreases in response to an increase of end-systolic pressure [86]. The velocity of the contraction of circumferential myofibrils (Vcf) is also a parameter that indicates the condition of the left ventricular systolic function. Similarly as the longitudinal systolic function, Vcf also decreases towards the end of the pregnancy, but never below the reference values. On the other hand, the pressure-load parameter—end-systolic wall stress (ESS) increases, especially in the third trimester, so the ratio between Vcf and ESS decreases [64, 87].

More precise data on the myocardial contractility are obtained using these parameters in patients who have a preserved EF (i.e., a preserved pump function of the heart), as the subendocardial layers of the LV are more sensitive to ischemia.

Most of the authors consider that there is depression of systolic function either as decrease of EF, SV and CO, either as decrease of longitudinal systolic velocity s′ [69, 78, 85].

It has been shown that regional longitudinal systolic function is markedly reduced in pre-eclamptic women, without regional systolic abnormalities in GH (had not observed an impact of the non-dipping pattern) [88]. Similarly, we have revealed that longitudinal systolic function is significantly reduced in women with GH and non-dipping pattern of BP, compared with both, normotensive pregnant women and those who developed GH with dipping pattern of

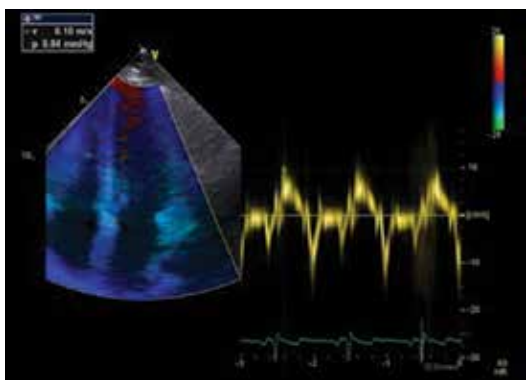

Figure 3. The longitudinal systolic function of the LV evaluated by tissue Doppler measurement—s′—longitudinal systolic velocity at mitral valve annulus.

BP, without the difference between normotensive and dippers in GH, as well as Vcf. Also, CO index was the most reduced, while Ees was the most increased in non-dippers [56].

7.2. Diastolic function in gestational hypertension/preeclampsia

The diastolic function is the ability of the LV to fill up to the normal end-diastolic volume, both at rest and in effort, with the mean pressure in LA ≤ 12 mmHg. The optimal function of the left ventricle depends on two cycles: its ability to relax and its compliance. Ability of the LV to relax, allows filling of the LV chamber from the LA in diastole. An increase in the chamber's compliance due to a sudden increase in pressure in the LV, enables the ejection of the SV into the arterial system in the systole. Since the LV relaxation process is more dependent on energy than the contraction of the heart muscle, it is logical that abnormalities of the diastolic function occur before systolic dysfunction in all situations in which myocardial circulation is compromised (ischemia, increased myocardial mass, hypertrophy) [89, 90].

If there is an increased need, for example during physical effort, pregnancy, the SV is increased without a significant increase in pressure in the LA [91]. This optimal situation is possible due to the cyclic interaction of myofilaments and the competence of the mitral and aortic valve [92]. Increased afterload will lead to decreased relaxation, especially if there is an increased preload, and this will contribute to increase of the LV filling pressure. This increase in pressure is the main consequence of the diastolic dysfunction [92, 93].

As it is mentioned, during pregnancy there is an increase in preload and myocardial mass. In hypertensive pregnancies, due to increased after-load and peripheral vascular resistance, hemodynamics is further complicated. There is a more pronounced decrease in the E/A ratio, prolongation of IVRT and DTE, changes of volume and dimensions of the LA [77–81]. In normotensive pregnant women, increased preload and decreased afterload lead to improved discharge of the LV during systole and reduction of end-systolic pressure. This results in a decrease of the pressure gradient between the LA and the LV, that reduces the required time for the drop of the pressure in the LV below the values of the pressure in the LA. As a result, filling of the LV in the diastole is done under the best conditions [25, 94]. In GH, increased afterload and TVR are followed by reduction in the LV discharge, leading to increased end-systolic volume and then to increased end-systolic pressure. This explains the prolonged IVRT because it takes longer time for the drop of the LV pressure below the LA pressure values. The delayed opening of the mitral valve and reduced LV compliance lead to reduced filling of the LV in the diastole.

It was revealed that diastolic function is more impaired in non-dippers with GH, compared to dippers, as well as global cardiac function and cardiac remodeling [56].

8. Conclusions

Recent studies have shown that the determination of the non-dipping pattern of BP, and therefore the role of ABPM, is of a great importance in women with GH.

Being an important risk factor for the remodeling of the LV in general population, the non-dipping profile of BP is also associated with a deterioration of maternal hemodynamics in GH. It is revealed that a depression of systolic function, an impaired diastolic function and remodeling of the LV are more pronounced in non-proteinuric women with non-dipping pattern of BP then in women with GH and dipping profile of BP. Besides, the non-dipping pattern was related with IUGR and preterm delivery.

According to the fact that, until nowadays, there are no data about the reversibility of these changes after delivery in the term on BP pattern, further research is needed to reveal that.138728

Conflicts of interest

None declared.

Abbreviations

A	peak velocity of the A wave
ABPM	ambulatory blood pressure monitoring
BP	blood pressure
DBP	diastolic blood pressure
DTE	deceleration time of the E wave
E	peak velocity of the E wave
Ea	effective arterial elastance
E/e′	index of the left ventricular filling pressure
Ees	left ventricular end-systolic elastance
EF	ejection fraction of the left ventricle
ESS	end-systolic wall stress
ET	ejection time of the left ventricle
ET1	endothelin 1
GH	gestational hypertension
HDP	hypertensive disoders in pregnancy
ISSHP	International Society for the Study of Hypertension in Pregnancy
IVRT	isovolumetric relaxation time of the LV

CO	cardiac output
GW	gestational week
HBP	home blood pressure
HR	heart rate
IUGR	intrauterine growth restriction
LA	left atrium
LV	left ventricle
LVEDV	left ventricle end-diastolic volume
MAP	mean blood pressure
mass	left ventricle myocardial mass
NO	nitric oxide
OBP	office blood pressure
PE	preeclampsia
SBP	systolic blood pressure
s′	longitudinal systolic velocity at mitral valve annulus
SV	stroke volume
TVR	total vascular resistance
Vcf	circumferential systolic velocity
WCH	white coat hypertension

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Chapter 6

Possibilities to Limit the Values of Clinical and Biochemical Parameters in Experimental Arterial Hypertension

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Additional information is available at the end of the chapter

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Abstract

The aim of this study is to estimate the influence of polyphenolic compounds, renin inhibitors (Aliskiren) and their association on clinical and biochemical parameters, on an experimental model of arterial hypertension (AHT). The combination of Aliskiren and polyphenolic extract has the effect of reducing systolic and diastolic blood pressure. Experimental data highlight the hypocholesterolemic, antiatheromatous, hypolipidemic and cardioprotective effects of polyphenolic extracts. The results demonstrate a significant decrease in the measured biochemical parameters of the oxidative stress (unspecific - ceruloplasmin, uric acid and enzyme - GSH-Px and SOD) of the groups treated with polyphenolic extracts. In the polyphenolically protected AHT group there are statistically significant differences compared to the AHT group, regarding the platelet adhesion index. Aliskiren has more evident vascular protective effects when associated with polyphenols in the experimental AHT compared to unprotected hypertensive group. The antioxidant properties of anthocyanins, combined with the vascular properties of these substances, recommend them as promising therapeutic agents in the prevention/therapy of cardiovascular disorders in general and of AHT in particular. The characterization of polyphenolic extracts, as well as the studies on biocompatibility, will constitute the baseline for understanding the mechanisms, by which phytopreparations can be used for preventive or adjuvant therapeutic purposes.

Keywords: systolic and diastolic blood pressure, aliskiren, polyphenolic extract, oxidative stress, lipid profile

1. Introduction

Hypertension, the most common cardiovascular disease, is the primary cause of stroke, coronary artery disease and sudden cardiac death. Hypertension, a major public health issue, is a

multifactorial disease dependent on complex interactions between genetic and environmental factors, yet many of these causes are not completely understood. Although there is a wide range of hypertension drugs available, a number of new antihypertensive drugs have been introduced during the last two decades. [1].

The renin-angiotensin-aldosterone system (RAAS) plays a pivotal role in the homeostatic regulation of blood pressure, fluid electrolytic balance, tissue perfusion and vascular growth. Pharmacologic blockade of the RAAS has proven to be an effective therapeutic strategy in the treatment of several cardiovascular disorders, including hypertension [2]. ACE inhibitors (ACEIs), which block the conversion of Ang I to Ang II, angiotensin receptor blockers (ARBs), which interfere with the Ang II binding to its type 1 receptors [3] and aldosterone antagonists, which inhibit the aldosterone action via the mineralocorticoid receptor (MR) receptor are considered RAAS-inhibiting drugs in clinical practice. Nonetheless, these agents do not allow the complete RAAS suppression since the negative feedback effect of Ang II on renin release is disrupted and consequently, the plasma renin activity and reactive activation of the RAAS increase.

Renin-like enzymes, such as cathepsin D or tonins, which occur in the vascular wall and release angiotensin I from angiotensinogen, are not blocked by renin inhibitors [4].

Aliskiren is the first direct orally active renin inhibitor [5, 6]. It is an effective hypertension drug with specific characteristics, among which we should mention its good renin-angiotensin system blocking ability, its long-lasting action, its pharmacological effects that outlive drug discontinuation and its positive tolerability as compared to placebo [7, 8]. The antihypertensive effect of aliskiren administered alone is similar or even better than that of other first-line hypertension agents. Moreover, its effect is considerably enhanced in combination with various other antihypertensive drugs and there are no adverse drug interactions [9–12]. Aliskiren is an extremely potent competitive inhibitor of renin. It has a high specificity for primate renin. This high specificity for renin makes it unlikely to produce adverse effects through interaction with other enzymes [13, 14].

Treatment of hypertension depends on the etiology of the disease and includes diet alterations, weight loss, exercise and pharmacological interventions. Pharmacological therapies (e.g., renin inhibitors, ACEIs, diuretics) that exist to treat hypertension are successful but they may be associated with negative side effects such as persistent cough, dry throat, allergic reactions, dizziness, angioedema and kidney failure. The popularity of nutraceuticals, which is another name for dietary supplements, has increased in hypertension treatment and prevention [15].

In addition to their high vitamin and fiber content, edible plants are also valuable since they are rich in polyphenols, which are antioxidant compounds responsible for some of the plants' color, flavor and healing qualities [16].

Phytodrugs having a complex composition develop superior qualitative effects compared to the drugs which specify the synthetic and semisynthetic chemicals. Some natural antioxidants, such as alkaloids, lycopene, phenolics, vitamin A/C/E, lipoic acid, and so on, are known

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to provide oxidation protection to biological components (e.g., DNA, proteins, lipids, etc.). In cardiovascular disease, neurodegeneration, inflammation, aging, metabolic syndrome and others, the level of oxidative stress is increased [17].

Natural polyphenols, obtained from many plants, have been shown to exert important actions on the cardiovascular system and may be a potential source of new compounds to treat cardiovascular diseases [18–21]. Observational evidence to date indicates that polyphenol-rich foods, in particular berries and dark chocolates, may influence cardiovascular disease risk factors [22–24]. The *Sambucus nigra* L. (elderberry) fruit extract is considered to be rich in primary polyphenols, leading to its high biological value [25].

2. The biochemical modifications of *S. nigra* extract on experimental arterial hypertension model

The French paradox undoubtedly emphasizes the effects of polyphenolics [17, 26], known as antioxidants, AMPK activator, ACE inhibitor and bioactive phytochemicals as they have many other biological benefits in addition to cardioprotection.

Scientists researching the medicinal benefits of the black elderberry plant have focused their work on the European species, *S. nigra.* The dark purple-black berries produced by this plant are rich in phytonutrients. It contains nearly four times the anthocyanins as compared to other commonly consumed berries. Elderberries are reported to include several bioactive compounds, both phenolic compounds like anthocyanin derivatives, including cyanidin 3-glucoside, cyanidin 3-sambubioside, cyanidin 3-sambubioside-5-glucoside and cyanidin 3,5-diglucoside [27–29] and triterpenic compounds such as ursolic and oleanolic acids and sterols such as β-sitosterol [30, 31].

2.1. The study of vascular reactivity by preliminary tests on the effects of a polyphenolic extract on *in vitro* isolated arterial fragments

Anthocyanins and some flavone (apigenin) and flavan-3-ol compounds may contribute to the prevention of hypertension. These vasodilatory properties may result from specific structural similarities (including the B-ring hydroxylation and methoxylation pattern) [32].

Polyphenol-rich extracts from fruits of *S. nigra* attenuate endothelial dysfunction induced by oxidative stress in mesenteric resistance arteries of rats.

Endothelial dysfunction, defined as the impairment of the endothelial-dependent relaxation by decreasing the nitric oxide (NO) bioavailability of endothelial origin, occurs through various mechanisms and is present in many pathological situations, and oxidative stress is often a major component of the pathogen mechanism, especially due to the fact that NO is inactivated by a reaction with various highly reactive molecular species containing oxygen (free radicals). The vasodilatory and antioxidant effects of polyphenols from various plant sources are well-known but there are relatively few *in vitro* studies

concerning their influence on vascular reactivity and endothelial dysfunction induced by oxidative stress [33–35].

Anthocyanins are powerful antioxidants that are found in significant amounts in the extracts that we investigate and may be responsible for the protective action observed *in vitro* [36–38].

Dried and powdered elder fruits (50 g) were extracted with 2 × 250 ml acidulated methanol (0.5% HCl) using a magnetic stirrer, each time for 1 h. The total phenolic content in elder fruit extract was determined by the **Singleton and Rossi method** [39]. The amount of total phenolic content was expressed as g gallic acid equivalents (GAE)/100 g extract. The result is the mean of triplicates ± standard deviation. The absorbance levels of all the solutions were determined by means of a UV–VIS Able Jasco V-550 spectrophotometer.

We used isometric myography to study the fragments of the first-order branches of the mesenteric artery from the rat. Endothelial dysfunction was induced by incubation for 15 minutes with 0.4 mM pyrogallol with or without the concomitant presence of the polyphenol-rich extract. All substances, including extracts obtained from the *S. nigra* fruit (SAMB), were administered in the organ bath (5 ml) as small volumes of stock solutions (50 μl). For the evaluation of the antioxidant effect, we used the primary stock solution (50 mg extract per ml DMSO), administered in 1/100 dilution in the organ bath; this is also the maximum dose used in other tests related to vascular reactivity.

We examined the protector potential of the studied extracts in terms of endothelial dysfunction induced through acute oxidative stress in isolated resistance arteries from rats (**Figure 1**).

The obtained results highlight the effects of the studied extracts on vascular reactivity, specifically following antioxidant protection in vitro and assessing according to its ability to attenuate the endothelial dysfunction induced by pyrogallol.

An immunohistochemical study performed by Kawa et al. [40] revealed that quercetin-3-O-glucuronide, one of the main quercetin metabolites in the circulatory system, accumulates in macrophage-derived foam cells of human atherosclerotic lesions but not in the normal aorta. It is still difficult to say whether some polyphenols accumulate in specific target organs; probably, the endothelium is likely to be one of the primary sites of flavonoid action.

2.2. Effects of polyphenolic extract, renin inhibitors and their association in arterial hypertension induced by deoxycorticosterone acetate (DOCA)-salt

S. nigra extract contains 6.9 ± 0.3% g polyphenols and 290.72 ± 4.02% mg anthocyanins besides other compounds. The dry polyphenol extract was diluted in 100 ml polyphenolic solution containing 840 mg natural polyphenols, 95 ml distilled water and 5 ml DMSO. The experiment used active therapeutic doses, well-determined fractions of DL50 on an experimental model of arterial hypertension.

Current preclinical studies were done on arterial hypertension models induced by DOCA-salt (deoxycorticosterone acetate-salt).

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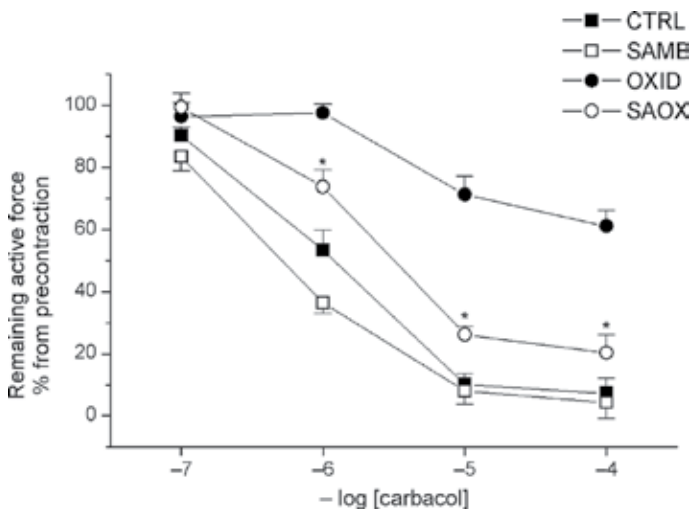

Figure 1. The carbazole-induced endothelium-dependent relaxant effect (CTRL) in the first-order branches from the mesenteric artery of the rat is inhibited by pretreatment with 0.4 mM pyrogallol (OXID) and is not altered by pretreatment with 0.5 mg/ml extract of *S. nigra* fruit (SAMB, $p > 0.05$). This extract attenuates the pyrogallol-induced endothelial dysfunction (SAOX; * $p < 0.01$ vs. OXID). N = 4 in all series; student test for grouped values.

2.2.1. The monitoring of heart rate, systolic and diastolic blood pressure

The monitoring of heart rate, systolic and diastolic blood pressure in the arterial hypertension experimental model was carried out with the **CODA™ noninvasive blood pressure system** [41] on white Wistar rats. American Heart Association (AHA) also recommends this method in its blood pressure measuring guide for laboratory animals. The actual experiment consists of carrying out at least six blood pressure measurements in each laboratory animal. The data collected should then be stored and processed using the CODA™ software.

The experiment was performed on the arterial hypertension model. The study was conducted on white Wistar rats with an average weight of 250–280 g, which were grouped in 6 groups of 12 (**Table 1**).

According to the provisions of the Federation for Laboratory Animal Science Associations on working with laboratory animals, all the rats were kept in 12 h light/12 h dark conditions with free access to water and food.

In the first stage, the *Shapiro-Wilk test* was done to confirm the normality of the specimens (groups); this was considered positive on exceeding the materiality threshold of 0.05 (if $p > 0.05$). Then *the descriptive statistics* were done for each group, including the *box-and-whisker* plots.

Aliskiren, which acts in limited steps against the RAAS, is a logical component in the mixed therapy because it increases the suppression of the RAAS and alleviates the reactive increase of the plasmatic renin activity when it is added to other antihypertensive agent classes. The mixed inhibition of RAAS might allow the usage of smaller doses of each component for obtaining a

Group **W**	Control group, contained normal animals, that did not receive natural polyphenols
Group **PS**	Animals that were administered polyphenols under the form of solution, from the extract obtained from the *S. nigra* fruit, with a dosage of 0.045 g/Kg bw, p.o. (by tube feeding), at every 2 days for 4 weeks;
Group **AHT**	Animals that were given s.c. DOCA-salt 20 mg/kg twice a week and NaCl (1%) added to the drinking water for 4 weeks
Group **AHT + PS**	Animals that were given polyphenols PS in the mentioned dosage at every 2 days p.o., together with DOCA-salt for 4 weeks
Group **AHT + Alisk**	Animals with AHT DOCA-induced that were given s.c. aliskiren 30 mg/Kg bw/day for 4 weeks
Group **AHT + Alisk + PS**	Animals with hypertension (AHT) that were given DOCA-salt and PS polyphenols in the dosage mentioned for 4 weeks

Table 1. Groups used in experimental model.

more efficient and more sustainable suppression of RAAS and probably with less side effects [16, 42].

Using the direct renin suppressor in the mixed therapy with polyphenolic *S. nigra* extract assures an enhanced protection and improves the results compared to monotherapy. The electrocardiographic aspect is significantly improved in the hypertensive group protected with polyphenols compared to the unprotected hypertensive group.

Experimental data indicate the fact that the polyphenol-rich extract is capable not only to effectively slow down the evolution of hypertension in the AHT experimental model but also to normalize the blood pressure levels in the group which received *S. nigra* extract, respectively, AHT + PS and AHT + Alisk + PS. The separate association of renin inhibitor and polyphenols in the hypertensive group reveals an improvement of the medium systolic blood pressure compared to the values obtained in the group which only received aliskiren. Similar data have been obtained for the diastolic component of blood pressure as well (**Figure 2**).

2.2.2. Biochemical plasma determinations (lipid profile, ceruloplasmin, uric acid and fibrinogen)

Polyphenol-induced AMPK activation suppresses lipogenic transcription factors (e.g., SREBP1/2, C/REBP, etc.) and enzymes (e.g., HMG-CoA reductase, acetyl-CoA carboxylase, etc.) for de novo biosyntheses of cholesterol and fatty acids and TG formation [43, 44].

In our study, the data underlined the fact that the lowest medium values of total cholesterol were recorded in hypertensive groups which received polyphenols (*S. nigra*) in addition to the renin inhibitor (aliskiren) (**Figure 3a**). Moreover, in order to support the lipid lowering effect of polyphenols, the mean triglyceride values detected were also lower in the groups which received *S. nigra*.

Due to the protection provided by polyphenols to the rats in the group AHT + PS, the LDL serum level is reduced, approaching the normal limits. Polyphenols have an important

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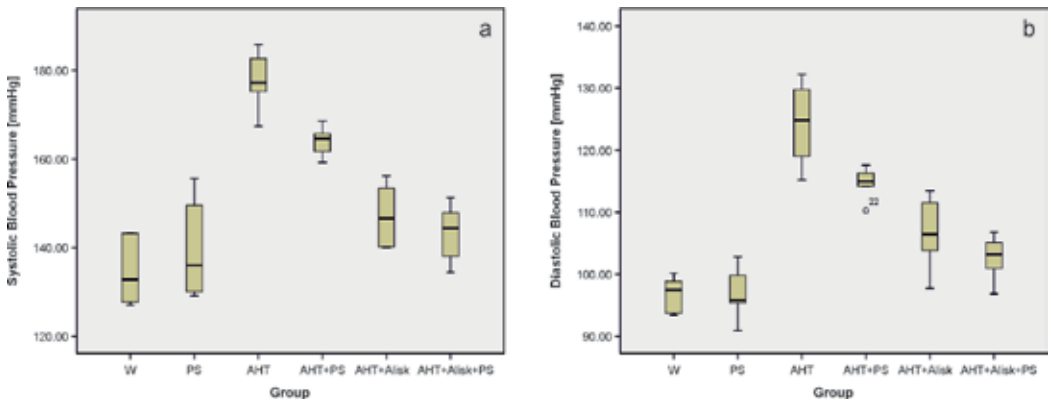

Figure 2. (a) The box-and-whisker plot of systolic blood pressure and (b) the box-and-whisker plot of diastolic blood pressure.

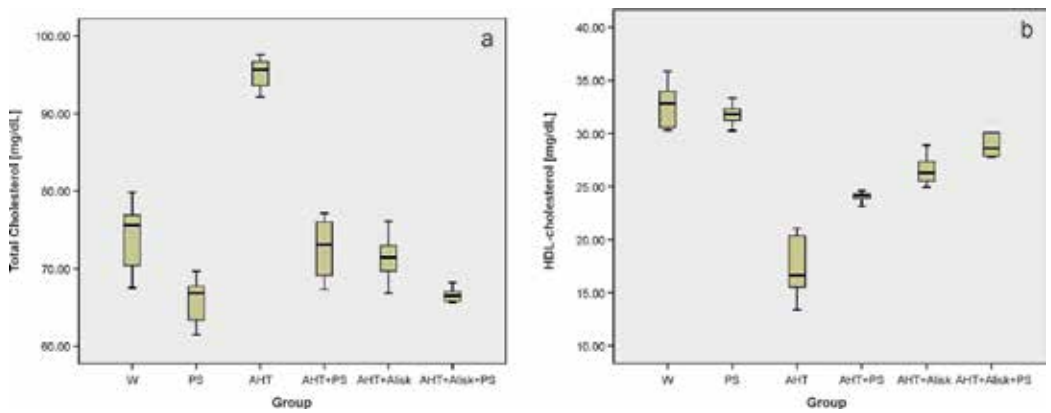

Figure 3. (a) The box-and-whisker plot of total cholesterol and (b) the box-and-whisker plot of HDL-cholesterol.

antiatherogenic role by their lipid lowering effect, especially by decreasing the synthesis and secretion of LDL and VLDL. In our study, HDL has significantly low values in the AHT group of rats compared to the rats in the W group and in the AHT + Alisk + PS group (**Figure 3b**).

Plasma proteins with high-molecular weight, such as ceruloplasmin, fibrinogen and C-reactive protein, have a powerful effect on red cell aggregation, a phenomenon found in hypertensive animals. In the experimental model we studied, the fact that the medium values of ceruloplasmin are higher in the other groups compared to the AHT group is to be noted, which suggests the beneficial antiradical effect of ceruloplasmin. *S. nigra* extract administration proved to be the most efficient, which determines the mean ceruloplasmin values close to those recorded with the control. By stimulating the ceruloplasmin activity, the effect of the polyphenols is favorable, proving their additional antioxidant role [45, 46].

The increase in the fibrinogen level generates modifications of the rheologic properties of the blood such as increased plasma viscosity, red cell aggregation, platelet thrombosis, alterations of the vascular reactivity and compromised endothelial integrity. The increase of fibrinogen concentration determines an increase of blood viscosity, which generates emphasized shear stress that activates endothelial cells and platelets. Thus, in our study, the highest mean values of fibrinogen are recorded in the AHT group, significantly higher than the other groups as well as fibrinogen-associated higher lipidic profile and heart rate.

Uric acid acts like a free radical scavenger due to the covalent bonds it can establish with the singlet oxygen. In animal models, hyperuricemia predisposes to high blood pressure by different mechanisms such as endothelial dysfunction, inflammation and vascular modifications at the renal microcirculation level, activation of the system renin-angiotensin-aldosterone. The data in our study is in line with that provided by the study [47], thus, the highest serum levels of the uric acid being registered in the hypertensive group. The lowest mean values of the uric acid are recorded in the groups treated with *S. nigra* and in the control group, significantly lower compared to those recorded in the other investigated groups.

2.2.3. Enzymatic determinations (SOD, CAT, GSH-Px) and nonenzymatic ones (GSH) regarding the antioxidant capacity

Antioxidative stress is mainly achieved by the classical antioxidation, which is also ensured by ACE inhibition interrupting AT-II-induced ROS generation and by the anti-inflammatory actions blocking inflammation-oxidation axis. The mechanisms involved in the antioxidant capacity of polyphenols include suppression of ROS formation by either inhibition of enzymes involved in their production, scavenging of ROS or upregulation or protection of antioxidant defenses [25, 48].

Polyphenol administration may offer indirect antioxidant protection by activating the endogen defensive systems and by modulating the cellular signaling processes such as NF-kB activation, glutathione biosynthesis and MAPK proteins [49]. The mechanism of polyphenols on vascular function depends on the ability of nitric oxide synthase (eNOS) and its bioavailability to the endothelium. This vascular nitric oxide regularity mechanism is believed to have involvement of polyphenols with kinase molecular signaling like PI3-kinase/Akt pathway and intracellular Ca^{2+} on eNOS phosphorylation which ultimately results in NO production [50].

Reduced glutathione (GSH) is an intracellular thiol antioxidant; lower level of this GSH causes higher ROS production, which results in imbalanced immune response, inflammation and susceptibility to infection [51].

GSH regeneration is provided by the enzymes in the pentose-phosphoric shunt, generator of NADPH (Zn-enzyme). GSH reacts with a wide variety of free radicals, having a free radical "scavenger" function and it contributes to the repair of the biologic disturbances mediated by radicals [52] (**Figure 4**). We did not record significant modifications regarding serum values of CAT in the AHT + PS, AHT + Alisk and AHT + Alisk + PS groups, compared to the control group.

The more the effects represent the total of their combined action, the more efficient is the activity of the antioxidants, each of them functioning according to different mechanisms and at

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various levels of the free radical evolution link in the organism. As a result, polyphenols have the possibility of adjusting and limiting the free radical or reactive species (peroxide) excess [53].

The results obtained following statistical analysis prove a significant modification of the measured biochemical parameters of the oxidative stress (nonspecific—ceruloplasmin and uric acid and enzymatic—GSH-Px and SOD) in the sense of decreasing oxidative stress in the one which was administered *S. nigra* extract.

When the AHT group was under polyphenol and aliskiren protection (the AHT + Alisk + PS group), the serum activity of SOD returned to normal values. As a result of the oxidative stress in the AHT group, serum activity of SOD has significantly lower values ($p < 0.001$) compared to those recorded with the W, AHT + PS and AHT + Alisk groups. We noticed that due to protection, the serum activity in the AHT + Alisk + PS group rats is more intense than in the case of the nonprotected AHT group (**Figure 5**). It should also be noted that, in the AHT group, low SOD values were noticed in association with low levels of ceruloplasmin and elevated levels of uric acid and fibrinogen.

Regardless of their antioxidant effect, polyphenols increase the production of vasodilator factors (NO, EDHF, prostacyclin) and inhibit the endothelin-1 synthesis with vasoconstrictor effect in the endothelial cells. Furthermore, it inhibits the expression of two major proangiogenic factors such as vascular endothelial growth factor (VEGF) and MMP-2 in smooth muscle cells.

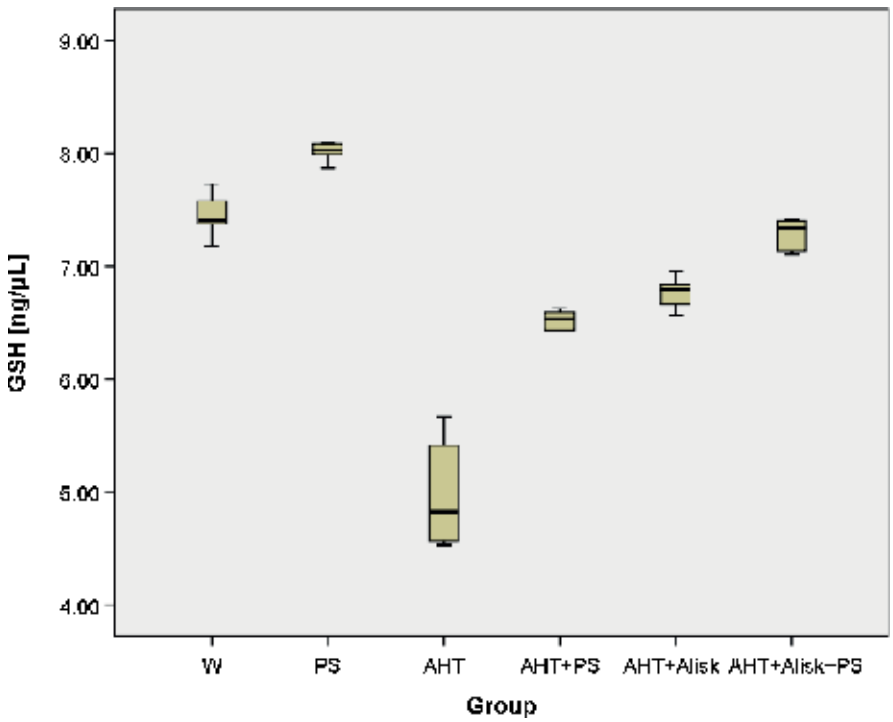

Figure 4. The box-and-whisker plot of GSH.

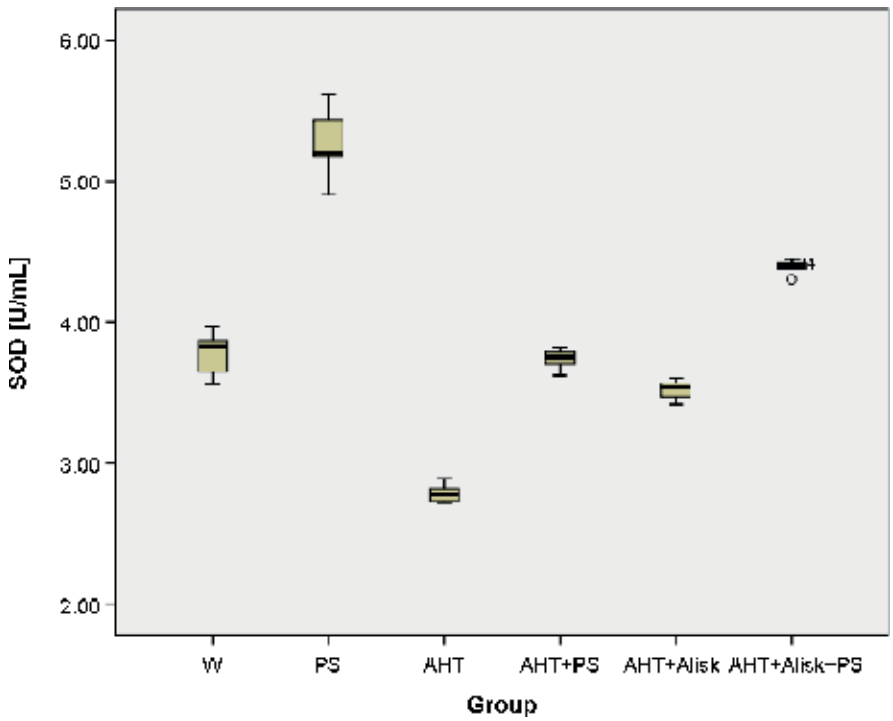

Figure 5. The box-and-whisker plot of SOD.

The changes in the redox status of the cell are determined by the endothelial dysfunction. Starting from previous studies that have discussed the potential antioxidant extract of *S. nigra* is proved that incorporation of anthocyanins from these fruits into endothelial cells causes protective effect against oxidative stress [54].

2.2.4. Platelet adhesion index determination

Activation of platelets adhering to the vascular endothelium induces the formation of lipid peroxidation and oxygen free radicals, which will inhibit synthesis of endothelial prostacyclins and NO. The effect of polyphenols in decreasing platelet activity has a strong impact on cardiovascular disease and can explain the epidemiological data on polyphenol function in cardiovascular disease [55, 56].

The main mechanisms by which flavonoids inhibit the platelet aggregation are: inhibition of phosphodiesterase with intracellular cAMP increase, cytoplasmic calcium reduction, cyclooxygenase inhibition, the enzyme involved in the transformation of arachidonic acid into TxA2, which is an aggregator and powerful vasoconstrictor [55]. In the AHT + PS group, there are statistically significant differences compared to the AHT group as well as to the control group (**Figure 6**). Platelet adhesion index (PAI) has been consistently correlated with the MDA level from the erythrocyte. Thus, there is a significant correlation between the intensity of the oxidative stress and the supplementation with the polyphenolic extract.

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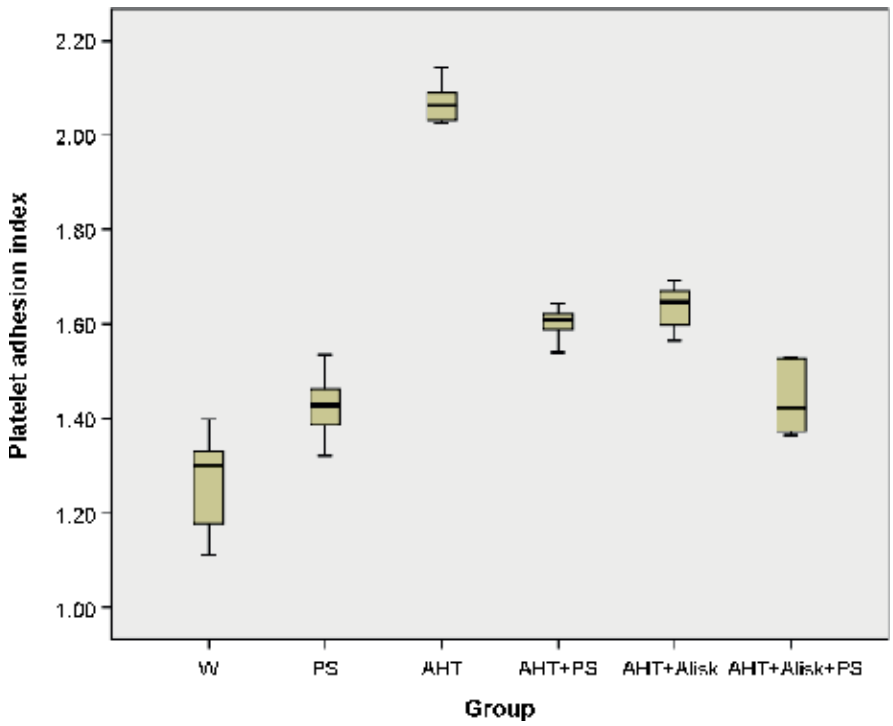

Figure 6. The box-and-whisker plot of platelet adhesion index.

The antioxidant properties of anthocyanins, combined with the vascular properties, characteristic of these substances, recommend it as promising therapeutic agents in the prevention/therapy of cardiovascular diseases in general and of AHT in particular.

Natural polyphenols and aliskiren may influence enzymatic and nonenzymatic changes in experimental arterial hypertension, in the sense of their favorable evolution, by improving lipid alterations and oxidative stress.

The potential cardioprotective properties of *S. nigra* extract include mainly antihypertensive, antiatherogenic and anti-inflammatory activities as well as inhibition of the platelet activation and aggregation, and attenuation of endothelial dysfunction. The main antihypertensive effects are the increase in NO bioactivity, the reduction of endothelin-1 and the decrease in ACE.

The obtained results show that antioxidant activity is all the more intense, as the polyphenolic preparation is administered for a long time during the course of the disease. Ensuring a diet rich in anthocyanins has beneficial effects on the whole body, the assumption being supported by the experimental data that highlight the hypocholesterolemic, antiatheromatosus, hypolipidemic and cardioprotective effects of polyphenolic extracts.

Mechanistically, it has been suggested that dietary polyphenols can alleviate hypertension through anti-inflammatory and antioxidant effects and increased oxide nitric (NO) production [16]. The anti-inflammatory effect is associated with a reduced expression of the redox-sensitive

nuclear factor-kB (NF-kB), while that the antioxidant effect of polyphenols is related to improved enzymatic activities of superoxide dismutase, catalase and glutathione peroxidase. In addition, polyphenols participate in the activation of the redox-sensitive phosphoinositide3 (PI3)-kinase/Akt pathway, leading to increased formation of NO [16]. Taken together, all these pathways help to reduce blood pressure in hypertensive conditions.

The dynamics of international scientific research on hypertension and on its complications materialized in the creation of preparations with a wide range of action and variable side effects, which require further investigations. These preparations are designed to have the widest possible action range, both as concerns their main action and as concerns their pleiotropic effects.

3. Conclusions

Subsequent studies will explore the potential of the direct renin inhibitors/(pro)renin blockers both in monotherapy and in combination with antihypertensive drugs of other classes, as well as their use not only to reduce arterial pressure but also for their renal and cardioprotective effects. In this respect, the characterization of polyphenolic extracts, as well as the studies on their bioavailability and biocompatibility, will constitute the baseline for understanding the mechanisms by which phytopreparations can be used for preventive or adjuvant therapeutic purposes.

By carefully extrapolating the experimental findings on animals to humans, the study could contribute to the increase of the life expectancy of hypertension patients and to the improvement of the life quality of the patients suffering from cardiovascular conditions.

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Chapter 7

Treatment-Resistant Hypertension: An Update in Device Therapy

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.76707

Abstract

Resistant hypertension (RH) is a clinical condition in which the hypertensive patient has become resistant to drug therapy and is often associated with increased cardiovascular morbidity and mortality. Several signaling pathways have been studied and related to the development and progression of RH: modulation of sympathetic activity by leptin and aldosterone, primary aldosteronism, arterial stiffness, endothelial dysfunction, and variations in the renin-angiotensin-aldosterone system (RAAS).

Keywords: resistant hypertension, signaling pathways, blood pressure, drug resistance

1. Introduction

Systemic arterial hypertension (SAH) stands out as the major independent risk factor related to cardiovascular disease (CVD) and remains the greatest modifiable risk factor, despite the important advance in the knowledge of its pathophysiology and availability of effective methods for its treatment. There are approximately 13.3 billion people with SAH in the world, and in developed Western countries, better controls are obtained on blood pressure (BP) levels.

Resistant hypertension (HAR) affects on average 30% of the adult population, about 1.2 billion individuals worldwide. Although the exact prevalence of HAR is still not established, it is estimated that this condition reaches 12–15% of hypertensive individuals.

2. Resistant hypertension

Resistant hypertension (RH) is characterized by a condition in which the patient requires four or more antihypertensive medications, including a diuretic, regardless of blood pressure control. RH patients can be classified as controlled or uncontrolled according to the achievement of the blood pressure goals [1].

The RH affects approximately 13–25% of the hypertensive population [2–4] and represents a risk factor for cardiovascular events. Results from the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) showed increased hazard ratios for stroke (1.57), end-stage renal disease (1.95), heart failure (1.88), coronary heart disease (1.44), and all-cause mortality (1.30) in RH compared to nonresistant hypertensive subjects [5].

RH is a multifactorial condition, and several environmental and genetic factors contribute to the development and progression of the disease. Firstly, the identification of pseudoresistance must be performed to identify true resistant hypertensive patients, caused mainly due to poor BP measurements, lack of adherence, suboptimal therapy, and white coat hypertension. In addition, secondary causes of RH, such as primary aldosteronism, pheochromocytoma, renal artery stenosis, or Cushing's syndrome should be identified since the pharmacological treatment will be specific for each condition. Among the factors associated with an increased risk for RH are: older age, African origin, female gender, overweight, and obesity [1, 6].

The RH presents three relevant characteristics: (1) high incidence of the following comorbidities: obstructive sleep apnea [7], thyroid disorders [7], primary aldosteronism [8, 9], reduced plasmatic renin activity, obesity [6], diabetes *mellitus* [1, 6]; (2) high prevalence of target organ damage; and (3) high blood pressure (BP) levels measured by ambulatory blood pressure monitoring (ABPM) [10–12].

The achievement of the BP goals relies on physician examination and on patient characteristics and compliance to pharmacological and nonpharmacological treatments. It is well know that obesity, excessive alcohol and/or salt intake, sedentary lifestyle, smoking, insulin resistance, difficulty in adopting dietary measures, and lack of adherence to therapeutic treatment affects BP control [12]. In addition, prescription of high-cost medicines by physicians, multiple administration regimens, suboptimal doses, and presence of adverse effects are associated with uncontrolled BP [13].

The factors associated with diagnostic and treatment of RH include lifestyle, detailed history of medication adherence, correct BP measurement, biochemical analysis for dosage of electrolytes, glucose, and creatinine, as well as determination of protein and sodium in the urine [12].

The exclusion of pseudohypertension is also necessary. For example, Mönckeberg's sclerosis is a condition characterized by the loss of elasticity and thickening of the walls of the muscular

Conditions	Obstructive sleep apnea	Primary aldosteronism	Renal artery stenosis	Renal parenchyma disease	Use of drugs and alcohol	Thyroid disorders
Diagnostic tests	Polysomnography	Serum aldosterone, plasma renin activity	Duplex Doppler ultrasonography, computed tomographic angiography, or magnetic resonance angiography	Serum creatinine	History taking	Thyrotropin, free thyroxine
Treatment	Continuous positive airway pressure	Spironolactone, eplerenone, or surgical resection of tumor in unilateral aldosterone-producing Adenoma	Renal revascularization in selected patients	Correction of underlying causes if possible	Discontinuation of offending agents	According to underlying disorders
Prevalence in RH (%)	60–70	7–20	2–24	1–2	2–4	<1
References	[7]	[8, 9]	[7]	[1, 7]	[1, 7]	[1, 7]

Table 1. Forms of secondary hypertension associated with RH (modified from Vongpatanasin [14]).

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arteries caused by a calcification of the tunica media constituted of smooth muscle. In the measurement of blood pressure by noninvasive methods, the patient presents high BP values, while in reality, the pressure is normal; therefore, it is necessary to use invasive measurement methods to correctly measure the BP [12]. In white coat hypertension, also a condition of pseudoresistance, the patient exhibits high values during the verification in the physician's office. It can be excluded by 24-h ABPM. It is estimated that 30% of patients with elevated BP and with treatment of up to three drugs present this condition of white coat hypertension [12, 14].

In order to complete the diagnosis of RH, there are some clinical situations that are considered as secondary causes of this condition, such as: primary hyperaldosteronism, pheochromocytoma, fibromuscular dysplasia, patients with increased risk of atherogenesis [12], obstructive sleep apnea, renal artery stenosis, renal parenchymal disease, Cushing's syndrome, and thyroid and parathyroid diseases [10]. These forms of secondary hypertension present high prevalence in association with RH, as can be verified in **Table 1**. Hyperaldosteronism results from the excessive production of aldosterone, a hormone that is produced in the adrenal glands and that decreases the excretion of sodium and increases the excretion of potassium by the kidneys, sweating, and saliva. The determination of the rate of aldosterone/renin ratio is used as screening tool for hyperaldosteronism diagnostic, and if any alteration is confirmed, diagnostic

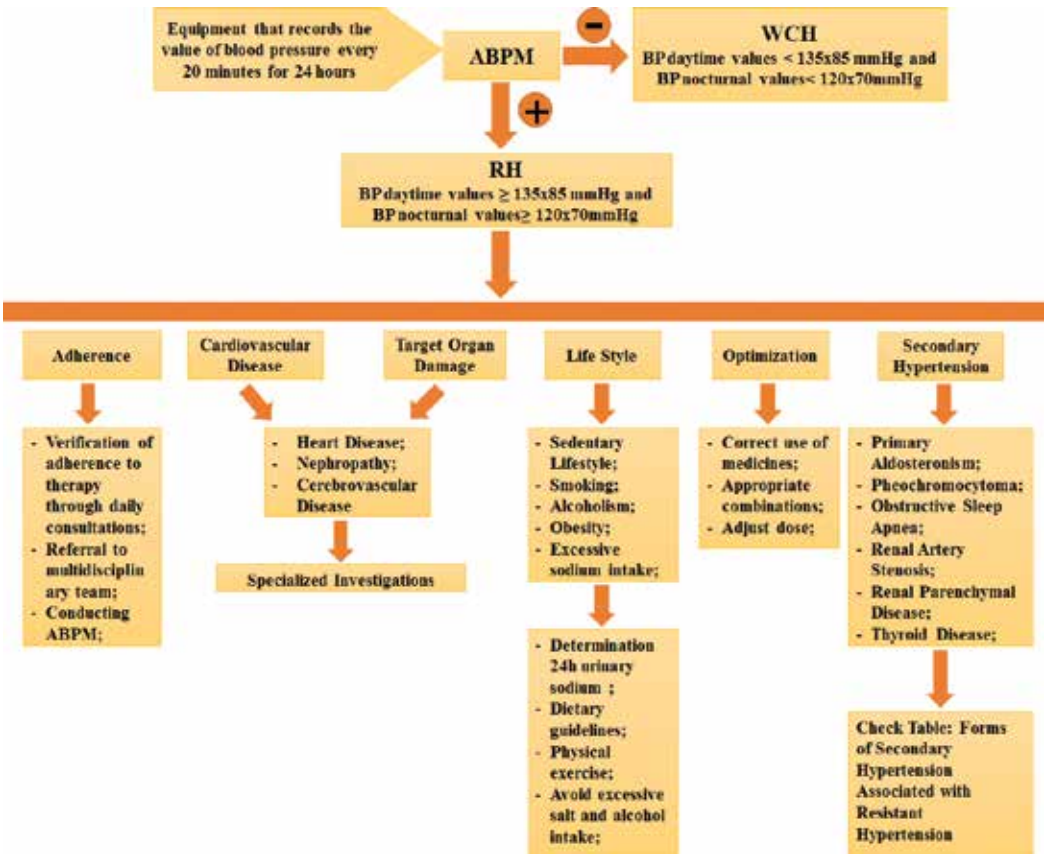

Figure 1. Recommendations for diagnosis of RH. Modified from Calhoun et al. [1] and Passarelli et al. [16]. Abbreviation: WCH, white coat hypertension.

imaging and blood samples from each side of the adrenal glands are used to corroborate the diagnosis [12]. Obstructive sleep apnea consists of the collapsing of the pharynx walls hampering the adequate respiration of the individual. The patient is then submitted to a nocturnal polysomnography in order to monitor respiration and body functions during sleep for diagnosing the condition [15]. For more information on diagnostic and treatment methods, see **Table 1** [14].

A flowchart (**Figure 1**) summarizes the steps involved in the diagnosis of RH according to the American Heart Association Statement [1, 16].

Although RH is a multifactorial condition, excess sodium, fluid retention, increased activation of the renin-angiotensin-aldosterone system, and higher sympathetic tone are among the most well-described mechanisms of BP elevation in RH. The complex pathophysiology of the development and progression of RH requires further investigation to identify molecular mechanisms that could be translated into diagnostic and more assertive therapeutic strategies. In the following sessions, the signaling pathways and the participation of miRNA in their regulation will be discussed.

3. Renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone system (RAAS) is responsible for the hemodynamic equilibrium. This is possible due to the effects of this system on the kidneys, which act in the sodium water balance, and also due to the influence in the vascular resistance on the peripheral blood vessels, thus permitting the maintenance of the BP [17]. In order to the RAAS to produce a response, it is necessary for some type of alteration to occur in the circulating blood volume, such as blood loss, dehydration, or even pumping failure by the ventricles [18] (**Figure 2**).

Juxtaglomerular apparatus comprises afferent arterioles in the distal part of the ascending branch of the loop of Henle in the renal glomeruli. The cells that line these arterioles in the region of the apparatus are called juxtaglomerular cells and are able to recognize the BP inside these vessels [18]. Moreover, the cells that line the loop of Henle in the region of the juxtaglomerular

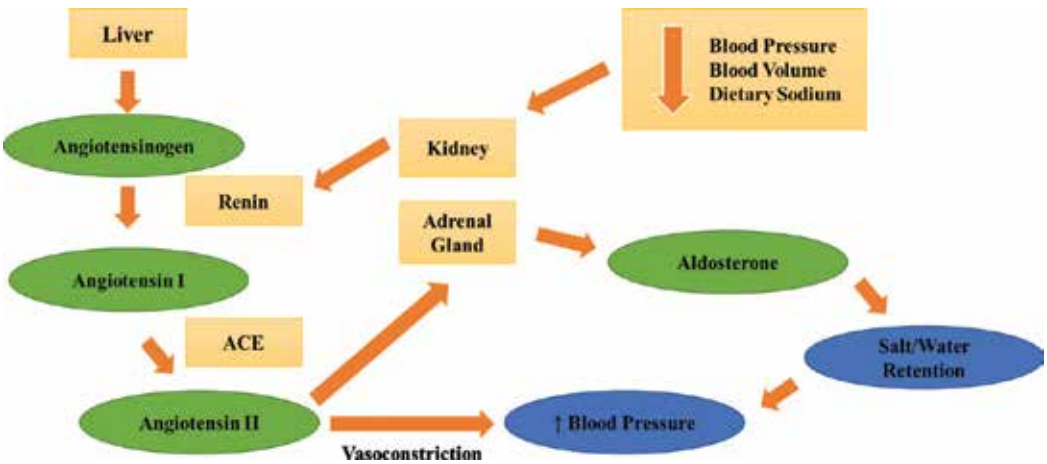

Figure 2. Hemodynamic control of RAAS. Modified from Maron and Leopold [18]. Abbreviation: ACE, angiotensin converting enzyme.

apparatus are called macula densa and respond to changes in the sodium concentration of the filtrate. By detecting these changes, the cells of the dense macula stimulate juxtaglomerular cells to produce an enzyme called renin that is released into the bloodstream. This enzyme is responsible for the production of angiotensin I (AngI) through the cleavage of angiotensinogen, which is synthesized and secreted by the liver. In the pulmonary and renal endothelium, an enzyme called angiotensin-converting enzyme (ACE), which hydrolyzes the circulating AngI in angiotensin II (AngII), is present. The angiotensin 1 receptor (AT1) is activated by AngII, thus promoting a vasoconstrictive response in the blood vessels, in addition to stimulating the adrenal gland to produce aldosterone. The renal tubules respond to the aldosterone by retention of sodium and water, which will promote increased blood volume and consequently, BP elevation [19, 20].

The RAAS constitutes the main signaling pathway involved in the long-term control of the BP. Innumerous regulators participate in this biochemical cascade of communication such as renin, angiotensinogen, AngI and II, ACE 1 and 2, and aldosterone and angiotensin- (1-7) [Ang-(1-7)]. The deregulation of one or more effectors of this system contributes to failures in blood pressure control, usually leading to hypertension [21]. Resistant hypertension is accompanied by intravascular fluid retention that can be attributed, at least in part, to dysregulation in the renin-angiotensin-aldosterone system. Previous studies have found evidence of intravascular volume expansion (higher levels of brain-type natriuretic peptide—BNP and atrial natriuretic peptide—ANP) and aldosterone excess (higher levels of plasma and urinary aldosterone, aldosterone to renin ratio) in resistant hypertension compared to controls [22]. Similarly, another study reported higher volume of fluid by thoracic electrical bioimpedance, suggesting that the intensification of diuretic therapy in those patients could be beneficial [23]. ANP and BNP are hormones that regulate cardiovascular hemodynamics. They are secreted by cardiac atria and cardiac ventricles, respectively, in response to stretch or pressure. Natriuretic effects are mediated by subtype A-natriuretic peptide receptor, which is expressed in several tissues, including kidneys, blood vessels, adrenal glands, and adipose tissue. ANP produces its natriuretic actions by increasing glomerular filtration rate and inhibits sodium transport in proximal tubule and inhibition of aldosterone release in adrenal cells. The latter effect is also attributed to BNP [24]. Aldosterone is one of the most studied RAAS components in RH; several studies had shown that aldosterone excess is a common characteristic of RH. In addition, primary aldosteronism is the most common secondary cause in the patients with RH [8]. This condition is characterized by excessive autonomic secretion of aldosterone by the adrenal gland, being the production of adenomas and idiopathic hyperaldosteronism in the main forms [25, 26]. This secretion, stimulated by renin, promotes the retention of sodium and water, promoting the elevation of blood volume, and consequently the increase of BP. When it is released into the bloodstream, the aldosterone diffuses through the membrane into the cytosol of renal tubular epithelial cells, subsequently binding to a family of NRC2-type mineralocorticoid receptors. This aldosterone-receptor complex will be translocated to the nucleus, activating the synthesis of proteins related to sodium and potassium transport, such as Na^+ K^+ ATPase (**Figure 3**) [27].

An important signaling pathway in the primary aldosteronism is the phosphoinositide 3-kinase (PI3K) pathway with the activation of mammalian target of rapamycin (mTOR), when overactivation is involved in the tumorigenesis and metastasis in some types of human tumors such as renal cancer, adrenal carcinoma, and pheochromocytoma [28–30] (**Figure 4**) [29]. The PI3K/AKT/mTOR pathway is regulated in response to the signaling of growth factors such as the epidermal growth factor (EGF) through receptor tyrosine kinases (RTKs) [31].

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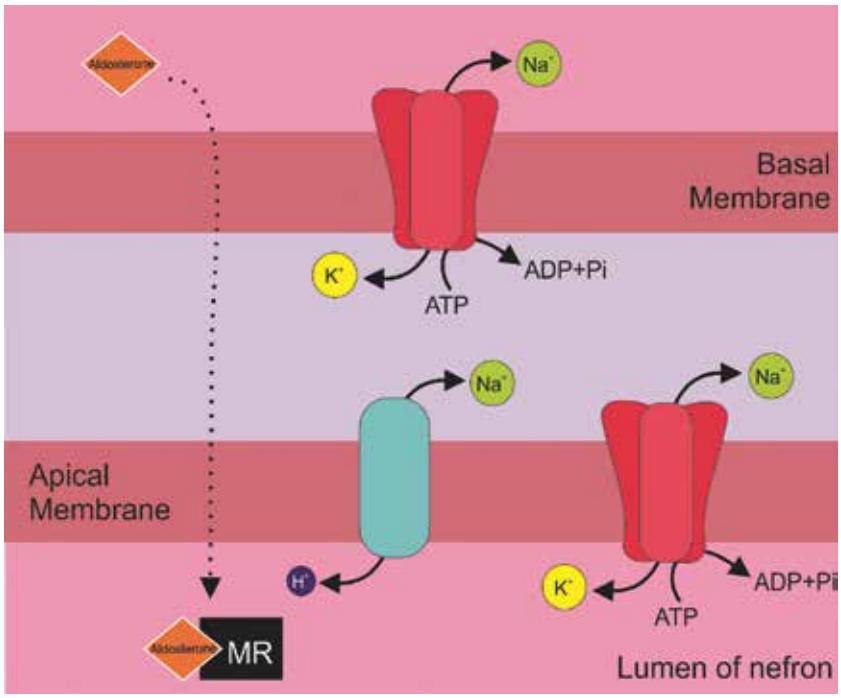

Figure 3. Signaling pathway of Na+/K+-ATPase activity and aldosterone.

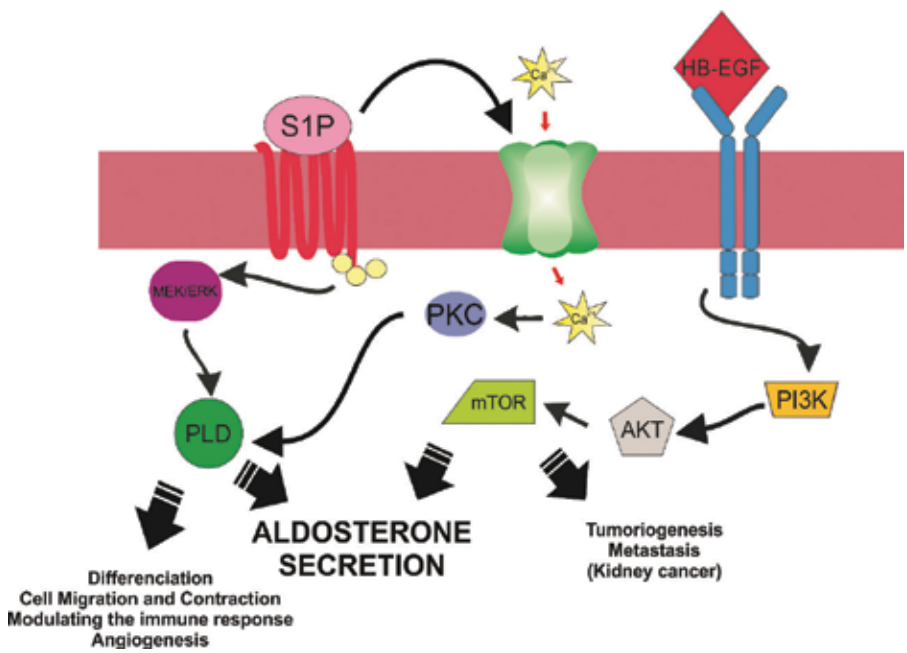

Figure 4. Signaling pathway involved in primary aldosteronism. Abbreviations: AKT, protein kinase B; EGFR, EGF receptor; ERK, extracellular regulated kinase; GPCR, G-protein coupled receptor; HB-EGF, heparin binding EGF; MAPK, mitogen-activated protein kinase; PIP2, phosphatidylinositol 4,5-biphosphate; PIP3, phosphatidylinositol (3,4,5)-triphosphate; PKC, protein kinase C; PLD, phospholipase; S1P, sphingosine-1-phosphate.

Another stimulus to the release of aldosterone is the action of sphingosine-1-phosphate (S1P) by means of the activation of the PI3K/AKT (protein kinase B) and mitogen-activated protein kinase (MEK)/extracellular regulated kinase (ERK) pathway in glomerular cells of the adrenal glands (**Figure 4**) [30]. S1P is a bioactive sphingolipid intracellularly formed that acts as a second messenger mediating regulatory processes such as cell differentiation, migration and contraction, modulation of immune response, and angiogenesis, and this molecule is considered to be the key hormone for hemodynamic stability in humans [32, 33]. Its action involves the activation of phospholipase D (PLD), calcium influx (Ca^{2+}) from the extracellular medium and phosphorylation of α and β isoforms of protein kinase C (PKC) [25, 26, 32].

Previous studies had shown excess of aldosterone in uncontrolled RH compared to controlled group. The same study demonstrated that aldosterone was correlated to arterial stiffness [34]. Furthermore, higher aldosterone levels were associated with the T allele for the polymorphism-344 C/T *CYP11B2* (aldosterone synthase gene) in RH subjects, and this effect was shown to be more pronounced in patients under spironolactone treatment [35]. Studies have demonstrated significant reductions in blood pressure with addition of mineralocorticoid receptors antagonists, such as spironolactone, and that drug has been suggested as the optimal fourth-line drug for BP control in RH.

Angio-(1-7) is a heptapeptide that carries out an important function in the RAAS. This molecule is formed both by the action of ACE 1 (dependent pathway) and the hydrolysis of AngII by the ACE 2 (independent pathway) [36, 37], being the last one in the most important pathway in the formation of Ang-(1-7) [38]. This molecule produces its AngII endogenous counter-regulatory effects on RAAS (vasodilation, cardio protection, natriuresis, and diuresis, angiogenesis inhibition, and cellular growth) [39] through the binding to its specific receptor called Mas, a G protein-coupled receptor [25, 40, 41].

The ACE2/Ang-(1-7)/Mas signaling pathway consists in one of the RAAS axes that opposes, in terms of function, to another classical axis of this system, the ACE/AngII/AT_1R. The imbalance of these two opposing axes, mainly in the direction of the ACE/AngII/AT_1R axis, predisposes to cardiovascular diseases and other disorders [37, 41].

The Ang-(1-7)/Mas complex regulates different signaling pathways, such as PI3K/AKT and ERK signal, and involves the maintenance of some effectors like nitric oxide (NO) [25, 41], FOXO1 (forkhead box 1) [39] and cyclooxygenase-2 (COX-2) [40] (**Figure 5**). Studies report that due to the participation of the Ang-(1-7) in these mechanisms, this heptapeptide is related to pathological conditions such as fibrosis and inflammatory processes in some organs, like lungs, liver, and kidneys [42]. Other findings demonstrate that Ang-(1-7), through the interaction with its Mas receptor, stimulates the activation of the nitric oxide synthesis (eNOS) in endothelial cells, promoting vasodilation [25, 36, 41].

Another study demonstrates that Ang-(1-7), through the interaction with its specific Mas receptor, promotes the increase in nitric oxide (NO) and prostaglandins (PG) synthesis and release, leading to vasodilation and inhibition of cellular growth, opposing to the vasoconstrictor and proliferative effects mediated by the interaction of AngII with its AT_1 receptors. The imbalance between these two axes of the RAAS, reflected by the imbalance between theses peptides, which are observed in cardiovascular diseases, can lead to the decrease in NO and consequently to endothelial dysfunction (**Figure 5**) [43].

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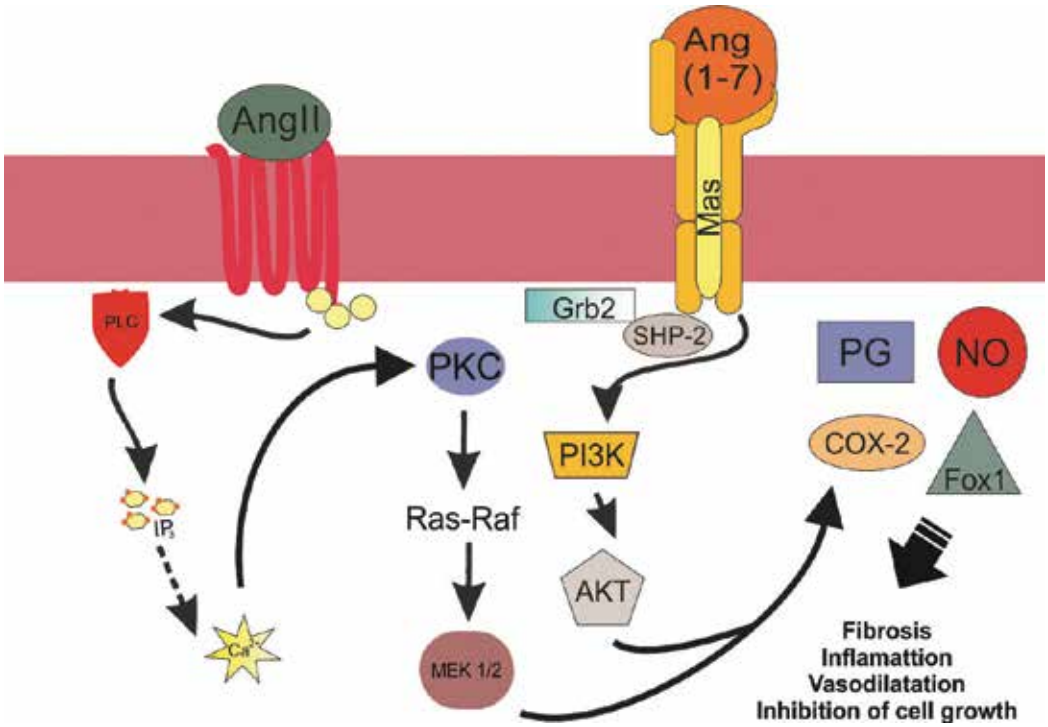

Figure 5. Signaling pathway of the SRAA axis. The figure shows the regulatory processes for the Ang-(1-7)/Mas in different signaling pathways, compared with the opposing RAAS classical axes of this system, the ACE/AngII/ATR. Abbreviations: AKT, protein kinase B; DAG, diacylglycerol; IP3, inositol triphosphate; PG, prostaglandin; PIP2, phosphatidylinositol 4,5-biphosphate; PIP3, phosphatidylinositol (3,4,5)-triphosphate; PLC, phospholipase C.

3.1. Sympathetic nervous system

Sympathetic nervous system regulates cardiac output and peripheral vascular resistance (vasoconstriction) through release of norepinephrine and epinephrine, resulting in increase in blood pressure. At the renal level, SNS activation increases renin release from juxtaglomerular cells and modulate tubular sodium reabsorption [44]. RH patients have reduced heart rate variability, which is a marker for SNS activity. It was shown that 63% of the patients present a non-dipping pattern (BP does not drop at night), which indicate sympathetic overflow. Moreover, sympathetic activation also increases sodium reabsorption and promotes renin secretion, and renal denervation has been investigated for the treatment of resistant hypertension. In spite first studies in humans had shown promising results, randomized and blinded clinical trials demonstrated no benefit on BP control compared to sham procedure [45]. Another intervention that has been tested is baroreflex activation therapy. Carotid sinus stimulation reduces BP in patients with uncontrolled RH, showing the import role of sympathetic activity in this condition [46–48].

3.2. Adipokines

Adiponectin and leptin are two of the adipokines produced in adipose tissue. Obesity is an important comorbidity in RH, and plasma levels of adiponectin and leptin were reported to be lower and higher, respectively, in RH [34, 49]. Leptin is a peptide hormone that is expressed

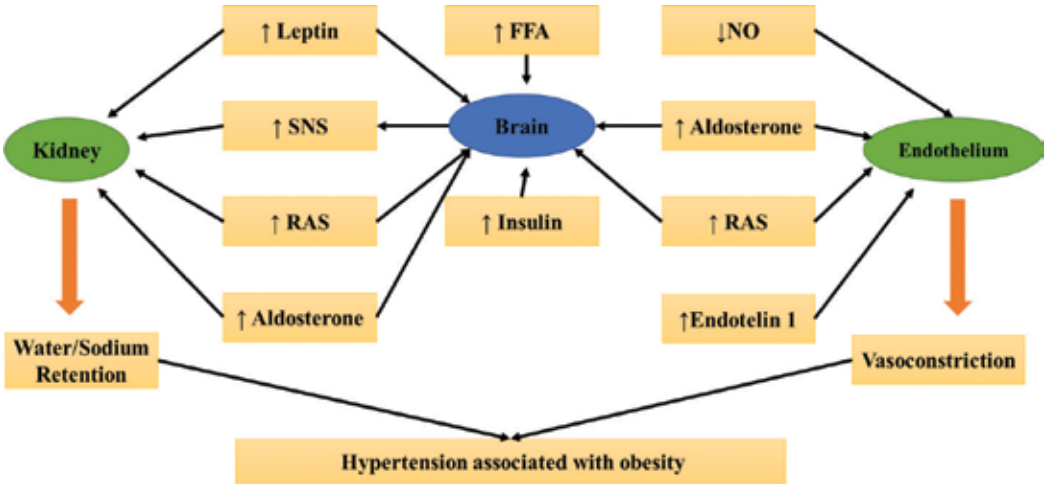

Figure 6. Signaling leptin pathway. The figure outlines the relationship between leptin and mechanisms involved in the neurons signaling as it stimulates the SNS, processes involved in pathogenesis of hypertension linked to obesity. Modified from Rahmouni et al. [51]. Abbreviations: FFA, free fatty acids; RAS, renin-angiotensin system.

in a variety of tissues, such as lymphoid tissue, pituitary gland, skeletal muscle, placenta, and ovary [50]. However, white adipose tissue is the main responsible for the synthesis and secretion of this peptide, which has effects to act on the hypothalamus in order to decrease appetite and stimulate sympathetic activity of the nervous system (**Figure 6**) [51]. Elevated levels of leptin stimulate neurons in the hypothalamus to secrete a precursor protein that is cleaved in α-melanocyte stimulating hormone, which binds to melanocortin 3 and melanocortin 4 receptors. The binding of this peptide to the receptors stimulates the sympathetic nervous system, elevates the energy expenditure, decreases food intake, and activates the hypothalamic-pituitary-adrenal axis [52–54]. A mechanism that demonstrates which factors are involved in the generation of hypertension associated with obesity is represented below (**Figure 6**) [51].

3.3. Insulin resistance and hypertension: the role of the caveolin-1 (*CAV1*) gene

It was recently demonstrated that the gene caveolin-1 (*CAV1*), located in the chromosome 7q31.1 [55], constitutes a gene that is associated with metabolic dysfunction in animal and cellular models, especially in insulin resistance, proving to be a potential marker for this condition in human beings [56]. Genetic variations in *CAV1* are involved in the mechanism of insulin signaling and vascular function (**Figure 7**), shown in studies with animal models and cell culture [57, 58].

Increase in homeostasis model assessment of insulin resistance (*HOMA-IR*) shows that *CAV1* is not only a genetic marker for dysfunction but also provides information about a potential mechanism of development of insulin resistance and hypertension in humans [56].

CAV1 is a regulatory gene for insulin signaling and insulin receptor stability [56]. Specifically, *CAV1* binds directly to the insulin receptor in the adipocytes and the disturbance of this complex by GM3 ganglioside causes alteration in insulin signaling [59] (**Figure 7**). In addition, the decrease in *CAV1* activity results in a 90% reduction in insulin receptor levels in the adipocytes of knockout rats [60].

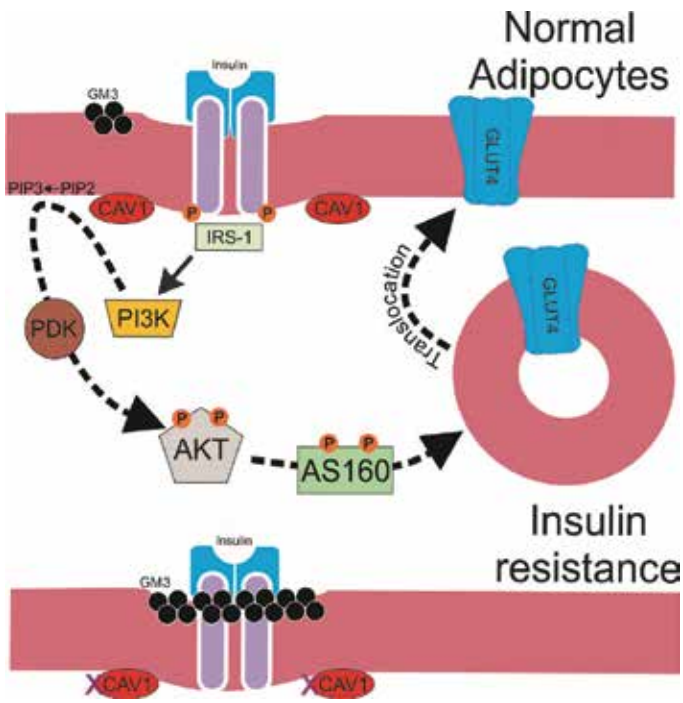

Figure 7. CAV1 signaling pathway. The stimulation of tyrosine kinase insulin receptor CAV1 signaling pathway leads to activation of PI3K resulting in translocation of the vesicle and exhibition of the GLUT4 in cell membrane. Abbreviations: AKT, Akt/protein kinase B; AS160, Akt substrate of 160 kDa; GLUT4, glucose transporter 4; GM3, ganglioside; IRS-1, insulin receptor substrate 1; PDK, phosphoinositide-dependent kinase-1; PIP2, phosphatidylinositol 4,5-biphosphate; PIP3, phosphatidylinositol (3,4,5)-triphosphate.

Although the role of *CAV1* in insulin-mediated glucose uptake is not well elucidated [60], this gene demonstrated relevance in the translocation of glucose transporter 4 (GLUT4) to adipocyte [61] and muscle cells [62].

3.4. Vascular stiffness and endothelial dysfunction

Previous studies have showed the participation of vascular stiffness and endothelial dysfunction in the pathogenesis of resistant hypertension. An increased carotid-femoral pulse wave velocity was observed in RH patients compared to non-RH hypertension, demonstrating the impairment of elasticity in these vessels. In addition, flow-mediated dilation was found to be reduced in RH, reflecting an endothelial dysfunction [63].

3.4.1. Epidermal growth factor receptor in the vascular smooth muscle

The activation of the signaling pathway of the epidermal growth factor receptor (EGFR) by matrix metalloproteinase (MMP), stimulated by G protein-coupled receptor (GPCR) agonists, such as catecholamines, endothelin-1 (ET-1) and AngII, leads to the increase of the oxidative stress, and promotes stimulation of the hypertrophic growth and consequently increase in the muscular tone in hypertension (**Figure 8**) [64]. Among these receptors, adrenoceptors and angiotensin receptors can be mentioned that contribute to the hypertension pathogenesis mainly through the vasoconstrictor effects produced after stimulation [65, 66].

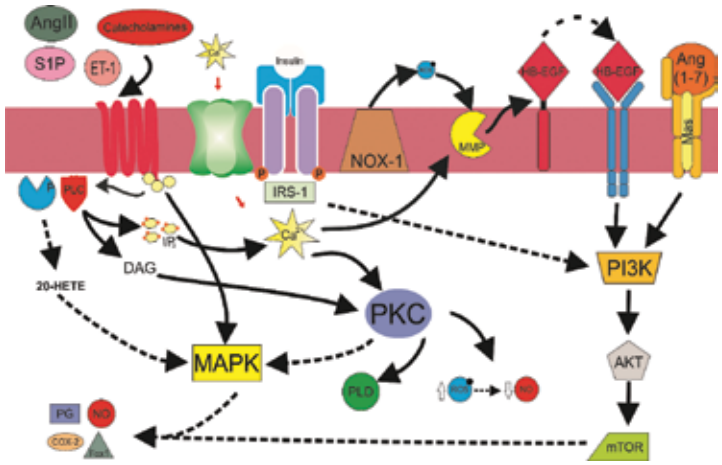

Figure 8. EGFR signaling pathway in vascular smooth muscle. The agonist action of the GPCRs stimulates NOX1 pathway and leads to the increase in the oxidative stress NOX1, which activates the signaling pathway of the EGFR. Abbreviations: AKT, protein kinase B; DAG, diacylglycerol; HB-EGF, heparin binding EGF; IP3, inositol triphosphate; NOX1, NADPH oxidase 1; PIP2, phosphatidylinositol 4,5-biphosphate; PIP3, phosphatidylinositol (3,4,5)-triphosphate; PLC, phospholipase C; ROS, reactive oxygen species.

The vasoconstrictor responses promoted by this pathway are mediated by phospholipase C (PLC), DAG, and Ca^{2+} besides the growth promotion pathway involving the tyrosine receptor and mitogen-activated protein kinases (MAPKs) (**Figure 9**) [67]. Studies have shown a connection between the GPCR stimulus with the MAPK signaling pathway (through the dependent activation of MPM) in the vascular smooth muscle cells [65, 68–70]. Associations

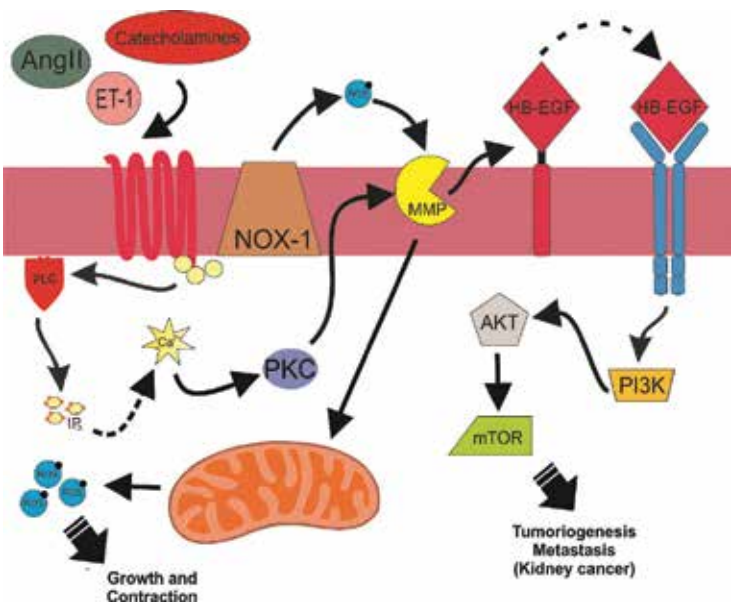

Figure 9. Signaling pathways involved in the development and progression of RH. The vasoconstrictor responses promoted by this pathway are mediated by phospholipase C (PLC), DAG, and Ca^{2+} besides the growth promotion pathway involving the tyrosine receptor and mitogen-activated protein kinases (MAPKs).

have been made between GPCR stimulus by MPM's such as MPM-2, MPM-3, and MPM-7 in cardiomyocytes, fibroblasts, and epithelial and endothelial cells [71] with consequent development of cardiovascular hypertrophy associated with hypertension [72–75] (**Figure 9**).

3.4.2. CYP4A (cytochrome P450-4A)/20-HETE (20-hydroxyeicosatetraenoic acid)

20-HETE is an arachidonic acid metabolite formed through reactions catalyzed by the cytochrome P450-4A enzymatic complex (CYP4A) in vascular smooth muscle cells and is related to vascular dysfunction and arterial hypertension (**Figure 10**) [76]. This molecule has vasoconstrictive action and exerts an important role in vascular function and in the development and progression of cardiovascular diseases [77]. Studies have demonstrated the relationship between genetic variations in precursors of 20-HETE formation and the elevation of this metabolite and the BP in humans [78, 79].

In Dahl SS (salt-sensitive) rats, a genetic model of salt-sensitive hypertension, 20-HETE has been shown to contribute to the increase in total peripheral resistance by reducing the ability of the vascular system to respond to direct vasodilation stimulation by reducing vascular function, thus contributing to an increase in BP [80, 81].

Some studies demonstrate that reactive oxygen species (ROS) are important molecules in the development of oxidative stress, playing an important role in vascular dysfunction in Dahl SS rats [82, 83]. The chronic exposure to low levels of AngII in these animals may lead to an increase in oxidative stress by elevating ROS cellular concentrations, thus contributing to the

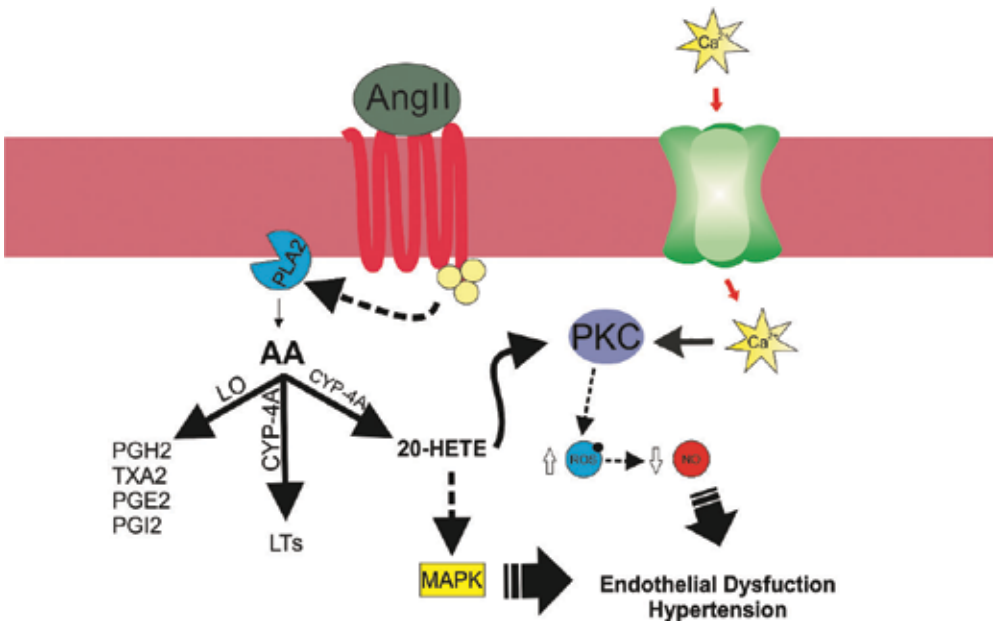

Figure 10. AngII stimulates signaling pathway through 20-HETE. The stimulation of GPCR by AngII agonist activates PLA2, which shoots the signaling intracellular pathway leading to activation of PKC as release calcium influx. Abbreviations: LO, lipoxygenase; LT, leukotriene; PGE2, PG E2; PLA2, phospholipase A2; PGH2, PG H2; PGI2, prostacyclin; ROS, reactive oxygen species; TXA2, thromboxane A2.

reduction of vascular relaxation even when these animals are submitted to a sodium restriction diet or are normotensive [84].

4. Concluding remarks and future directions

Due to the difficulty of studying RH in animal and *in vitro* models, the studies are clinical and poorly understood in terms of mechanisms. Thus, we decided to describe the microRNAs that interact with the most relevant pathways in RH. To date, several miRNAs have been identified and are related to the complications of resistant hypertension.

Epigenetic as well as genetic factors are identified every day and they are associated with variation in blood pressure levels. As reviewed herein, mutation polymorphism in some signaling pathway gene may increase or decrease the expression of some microRNAs, which are involved both in RH development and therapy response as RH-associated complications such as renal failure, coronary artery disease, cardiac hypertrophy, stroke, and among others. Therefore, the use of microRNA as biomarkers in prevention, diagnosis, and therapy of this disease may help to understand the disease, improve pharmacology therapy as well as prevent complications.

Conflict of interest

The authors declare that they have no conflict of interests relating to this paper content.

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Chapter 8

Resistant Hypertension

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Additional information is available at the end of the chapter

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Abstract

The most common causes of therapeutic failure in hypertensive control are undiscovered secondary causes of hypertension and lack of patient/doctor compliance. In about 10% of cases, it can be attributed to resistant hypertension caused by a hyperactivity of the sympathetic nervous system, condition with a high cardiovascular risk to the patient. Resistant hypertension is failure to diminish blood pressure values to <140/90 mmHg (<140/85 mmHg for diabetic patients) with a lifestyle method and prescription of least three antihypertensive drugs in optimal doses, including a diuretic, or when patients use four or more antihypertensive drugs regardless of blood pressure control. Patients with resistant hypertension are typically presented with a long-standing history of poorly controlled hypertension. Early diagnosis and adequate treatment are needed to avoid end organ damage and to prevent cardiorenovascular remodeling. Cardiorenovascular morbidity and mortality are significantly higher in resistant hypertensive population. The need for the individualization of therapy and the use of the management strategies are also given weight in the treatment of resistant hypertension patients, including optional, innovative therapies, like a renal denervation or baroreflex activation. New innovative device therapies create an additional novel pathway of blood pressure-lowering procedures and should be prescribed by a specialist hypertension clinic.

Keywords: resistant hypertension, adherence, cardiorenovascular risk, sympathetic activation, innovative device therapies

1. Introduction

Hypertension is chronic disease and is extremely complex. Hypertension has the largest prevalence of 30–45% of all cardiovascular risk factors. The achievement of blood pressure values below 140/90 mmHg is considered one of the main methods of achieving high long-term patient quality of life. Hypertension has an extreme phenotype, especially resistant

hypertension. Genetic factors may play a great role. Some genes have been associated with failure to antihypertensive medication treatment. Environmental factors contribute to the development of resistant hypertension—making importance of epigenetic. Resistant hypertension is a consequence of different pathophysiologic processes that are associated with high cardiovascular risk as consequences of increased stimulation of renin-angiotensin system and aldosterone production [1]. Arterial stiffness and atherosclerotic disease are also common in resistant hypertension patients. If pharmacological therapy with at least three antihypertensive drugs in optimal doses, including a diuretic, fails to reduce the office blood pressure to below 140/90 mmHg, patient suffer from drug-resistant hypertension [1, 2]. There are two types of drug-resistant hypertension: controlled and uncontrolled. Uncontrolled resistant hypertension patients cannot achieve blood pressure under 140/90 mmHg despite the use of three and more antihypertensive drugs (one of them being diuretic) and optimal lifestyle changes. The prevalence has been estimated between 8 and 13% of all antihypertensive drug-treated patients [2]. In last 50 years, the use of antihypertensive drugs has revolutionized the therapy of hypertension. Despite the available pharmacological inhibition of the sympathetic nervous system, about 50% of patients show suboptimal control, and pharmacotherapy does not provide adequate effects in everyday clinical practice [3–5]. The most common causes of therapeutic failure are undiscovered secondary causes of hypertension and lack of patient/doctor compliance. In about 10% of cases, it can be attributed to resistant hypertension caused by a hyperactivity of the sympathetic nervous system [6]. Overactivity of the sympathetic nervous system is a condition that confers a high cardio(reno)vascular risk to the patient [7, 8]. Renal sympathetic denervation produces multilevel inhibition of the sympathetic nervous system and triggers additional positive metabolic effects [9–11]. According to the results of different trials with renal sympathetic denervation for control of resistant hypertension, including Symplicity HTN-3, renal sympathetic denervation seems to be safe, and procedure-related complications of catheter-based renal sympathetic denervation were rare. Symplicity HTN-3 study did not show differences in systolic blood pressure reduction between treatment and control groups, but in the context of the study characteristics and the way it was conducted, there are several concerns about inexperienced doctors in the field of renal sympathetic denervation, the study population, and the medical treatment [11, 12]. Baroreceptor activation therapy or baropacing can be applied in patients with treatment-resistant hypertension too. When baroreceptors sense an increase in carotid transmural pressure, they respond by inhibiting sympathetic and stimulating parasympathetic centers in the brainstem [13]. Additional devices could be an option for patients with side effect of available antihypertension medications too control blood pressure.

2. Prevalence and etiology of resistant hypertension

The prevalence of resistant hypertension is unknown: epidemiological researches on resistant hypertension are missing. The data of frequency can be taken out from observational and big controlled clinical studies and is between 10 and 30% among patients with hypertension. Etiology of failure to diminish systolic and diastolic blood pressure with a therapeutic plan

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that includes lifestyle modification and prescription of at least three different drugs in optimal doses is heterogeneous. First it is very important to understand the difference between uncontrolled (pseudoresistant or apparent) and real resistant hypertension. Potential very common reasons for uncontrolled but not resistant hypertension are weight gain (obesity, body mass index >30 kg/m^2), poor adherence, and the use of drugs such as nonnarcotic analgesics and nonsteroidal anti-inflammatory agents by mechanism of causing sodium retention. Other lifestyle factors that are associated with resistant hypertension are excessive dietary sodium intake and heavy alcohol intake. Secondary causes include unrecognized/untreated obstructive sleep apnea, primary aldosteronism, chronic parenchymal kidney disease, renal artery stenosis, and diabetes. Uncommon causes are pheochromocytoma, Cushing's disease, aortic coarctation, and intracranial tumors. The most common causes of pseudoresistance are poor adherence to antihypertensive therapy, white-coat effect, inaccurate measurement of blood pressure, pseudo-hypertension, and elderly patients [14, 15]. Other factors contributing to nonadherence with antihypertensive medication are African American race, gender (women tend to exhibit more nonadherence than men), higher adverse event incidence, polypharmacy, and higher drug costs. Poor adherence to antihypertensive therapy is the most important cause of unsuccessful blood pressure control. Analyses show that approximately 40% of patients will not continue their antihypertensive medications during the first year after diagnosing resistant hypertension. During 5–10 years of follow-up, those numbers reach 60% [16].

Inaccurate blood pressure measurement is not uncommon; it occurs when patients are not instructed to sit calmly and quietly and when the cuff is too small [17]. In diagnostic algorithm of resistant hypertension, stepwise approach is recommended. First is the optimization of control of blood pressure by excluding other causes of pseudoresistance. Very common cause of pseudoresistance is hypervolemia due to excessive sodium intake/retention, impaired kidney function, heart failure, and ineffective use of diuretics. Activity of neuronal sympathetic system which can be produced by chronic stress/pain, hypertension provoked by fear, hyperventilation, and vasoconstriction is an additional cause of pseudoresistance. The use of drugs like nonsteroidal anti-inflammatory agents, glucocorticosteroids, licorice, erythropoietin-stimulating agents, cyclosporine or tacrolimus, antidepressants, sympathicomimetics, oral contraceptives with estrogen, anti-VEGF, cocaine, and amphetamines are very often unrecognized cause of pseudoresistance. Undiagnosed secondary hypertension due to kidney diseases, renal artery stenosis, obstructive sleep apnea, or endocrinological disorders is the secondary common cause of pseudoresistant hypertension. Inappropriate blood pressure measurement and white-coat hypertension have to be excluded before diagnosis of true resistant hypertension. Suspicion of resistant hypertension requires an analysis of drugs which in the hypertensive patient is treated with.

3. Risk factors for resistant hypertension

Hypertension is one of the leading modifiable factors in cardiovascular continuum. A hyperactivity of the sympathetic nervous system is a condition that confers a high cardiovascular risk to the patient. Resistant hypertensive patients often have comorbid cardiorenovascular

conditions, such as heart failure, atrial fibrillation, and chronic kidney disease. Studies have documented independent contribution of sympathetic activation to the cardiorenovascular disease [18, 19].

Cardiovascular risk doubles with increase of 20 mmHg systolic blood pressure and 10 mmHg diastolic blood pressure [20]. Particularly high cardiovascular risk is in patients with high systolic blood pressure and normal or low levels of diastolic blood pressure. Patients with chronic kidney disease and diabetic patients are special population with high cardiorenovascular risk. We do not know the real prevalence of chronic kidney disease in patients with resistant hypertension, and the prevalence of resistant hypertension in chronic kidney disease (I–IV stages) patients is also underestimated [6]. Obesity as well as chronic kidney disease could be the reason of resistance. Other risk factors that are usually related with resistant hypertension have a synergistic effect in development and worsening of resistant hypertension. Target-organ damage such as retinopathy, vascular dementia, chronic kidney disease, and left ventricle hypertrophy supports a diagnosis of poorly controlled resistant hypertension.

3.1. Cardiovascular risk in resistant hypertension

Higher cardiovascular risk is noted in patients with resistant hypertension and diabetes or chronic kidney disease compared to general hypertensive population [19]. If we compared with the nonresistant hypertension patients, the resistant hypertension patients had a greater prevalence of comorbid conditions like diabetes mellitus (48% vs. 30%), chronic kidney disease (45% vs. 24%), ischemic heart disease (41% vs. 22%), and cerebrovascular disease (16% vs. 9%; $P < 0.001$ for all) [19]. Sim and coauthors showed that patients with uncontrolled resistant hypertension (61.7%) are more frequent than controlled. When compared with controlled resistant hypertension patients, uncontrolled were at a greater risk for cerebrovascular and end-stage renal disease. The risk of end-stage renal disease and cerebrovascular disease was 25% and 23% greater, respectively, supporting the linkage between blood pressure and both outcomes [19].

4. Diagnostic workup of resistant hypertensive patients

To determine true resistant hypertension, there is a need to exclude secondary causes of resistant hypertension like obstructive sleep apnea, atherosclerosis, and renal or hormonal disorders [2]. Diagnostic workup includes clinical examination, laboratory testing, and diagnostic methods to identify target organ damage as it is proposed by the European Society of Hypertension/European Society of Cardiology [8]. Pseudoresistant hypertension should not be confused for the real one in order to avoid unnecessary diagnostic procedures and treatments. Treatment of resistant hypertension involve the correct pharmacological approach, reduce therapeutic inertia (the physician), and involve taking medications regularly that have been proven to be effective and well tolerated (the patient). Patients have to be engaged in their management. There is the need for regular adherence with the prescribed regimen. We need diagnosis-based approach that takes into consideration not only a person's blood pressure but also the overall cardiovascular risk [19, 20].

4.1. Medical history and clinical examination

The medical history should document duration, severity, and progression of the hypertension, treatment adherence, and response to prior medications, including adverse events. Very important in medical history is current medication use, including herbal and over-the-counter medications. Loud snoring, daytime sleepiness, and witnessed apnea indicate obstructive sleep apnea. A history of peripheral or coronary atherosclerotic disease and worsening kidney function are suspicious for renal artery stenosis. Labile hypertension followed by palpitations and diaphoresis indicates the possibility of pheochromocytoma. In physical examination, carotid, abdominal, or femoral bruits indicate artery stenosis. Moon facies, abdominal striae, and central obesity suggest Cushing's disease. Diminished femoral pulses and difference between arm and thigh blood pressures are suspicious for aortic coarctation and/or aortoiliac disease.

4.2. Biochemical evaluation

Biochemical evaluation should include routine metabolic profile such as sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, albumin/creatinine ratio, and estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation and urate level. Reporting of estimated glomerular filtration (eGFR) rate is of most importance in recognition of early stages of chronic kidney disease characterized with slightly or moderately reduced eGFR and serum creatinine values usually within the population-based reference intervals [6]. Even in the setting of ongoing antihypertensive treatment, the ratio of aldosterone and renin is a useful diagnostic tool for primary aldosteronism, although such high ratio has low specificity and high negative predictive value. Additional analysis includes cortisol in 24-h urine and plasma cortisol. A 24-h urine collected during ingestion of the patient's normal diet can be helpful in estimating dietary sodium and potassium intake. Measurement of 24-h urinary metanephrines or plasma metanephrines is an effective screen for patients in whom pheochromocytoma is suspected.

4.3. Diagnostic methods

Numerous biological and lifestyle factors can contribute to the development of resistant hypertension. Some of them are the following: drugs, obesity or volume overload, diabetes, older age, renal diseases, aldosteronism, and obstructive sleep apnea. Less frequent are pheochromocytoma, Cushing's syndrome, thyroid diseases, and aortic coarctation. In diagnostic approach to resistant hypertension, history of a patient is very important, as well as his former adherence, adequate measurements of blood pressure, physical state, biochemical tests, and noninvasive imaging. It is of high importance that the evaluation of a patient includes 24-h ambulatory monitoring of blood pressure (AMBP). "Non-dipper" rhythm in AMBP can be often found in high-risk patients, such as chronic kidney patients and patients with obstructive sleep apnea.

The French Society of Hypertension gave the following recommendations for diagnostic approach to resistant hypertension: (A) standardized device and an appropriate cuff size should be used to avoid poor blood pressure measurement; (B) white-coat effect should be eliminated by ambulatory or home blood pressure measurement. Thresholds for uncontrolled

hypertension are home blood pressure measurement ≥135/85 mmHg, 24-h ambulatory blood pressure measurement ≥130/80 mmHg, daytime ambulatory blood pressure measurement ≥135/85 mmHg, and nighttime ambulatory blood pressure measurement ≥120/70 mmHg; (C) it is necessary to determine if the optimal triple-drug therapy is prescribed; (D) poor patient compliance should be assessed using a questionnaire, during drug analysis and pill count; and (E) it is suggested to search for factors that could influence treatment resistance (e.g., obesity, excessive dietary sodium intake, alcohol, drug interactions) [21]. If the diagnosis of resistant hypertension is confirmed, the patient should be referred to a hypertension specialist. After true resistant hypertension is confirmed, evaluation should include identification of the underlying cause and assessment of cardiovascular risk and end organ damage. Doppler of renal arteries, magnetic resonance angiography, or computed tomography angiography are highly recommended to assess the anatomy before renal sympatric denervation [21, 19].

5. Treatment strategy of resistant hypertension

Treatment strategy selects the best therapeutic options including lifestyle modifications and pharmacological and interventional treatment.

5.1. Lifestyle modifications

Definition of poor or unhealthy lifestyle is sedentary, overweight smoking, or drinking subjects with no exercise habits, on high-salt diet, with negative feelings about medicine [6]. More than 60% of patients with resistant hypertension are overweight and obese (12% BMI >40 kg/m^2) [6]. In both men and women, elevated blood glucose levels, hypertension, obesity, and hypercholesterolemia are among the leading risk factors contributing to death and illness. In an assessment of environmental, occupational, and metabolic risks contributing to death and disability, the study reports that tobacco was responsible for more than 7 million deaths and poor diet could be blamed for approximately one of five deaths. Appropriate lifestyle and dietary measures, smoking cessation, and weight reduction are highly recommended in patients with hypertension [22]. However, little is known about passive smoking and secondhand smoke and about the relationship between passive smoking and cardiovascular risk factors. Wu and authors found the positive association between passive smoking and blood pressure or hypertension [22]. Higher levels of physical activity have been linked to a lower risk of cardiovascular disease and diet. Authors from the Prospective Urban Rural Epidemiology (PURE) study, which is one of the world's largest epidemiological studies, find that the form of physical activity has no difference [23]. All of physical activity types are of benefit in reducing the risk of cardiovascular disease and premature death. The benefits of increased physical activity were seen regardless of whether that activity was recreational, occupational, or domestic [23].

5.2. Adherence

Adherence to antihypertensive medication is a key modifiable factor in the management strategy of hypertension. The nature of adherence is multidimensional. Blood pressure control has

to be multicomponent and patient-centered interventions to improve adherence. Strategies to improve antihypertensive medication adherence and blood pressure control include a multilevel approach that combines strategies at the level of the patient and healthcare provider, organization, and system. Very important are communication skills with hypertension patient, information exchange, and simplification of therapy. It is recommended to prefer antihypertensive agents with 24-h blood pressure control in once daily dose and fixed dose combination. Very important is low cost of antihypertensive agents, especially in low-income patients. Tele-health strategies; the use of experienced health professionals for intervention devices, especially in the field of renal sympathetic denervation; and self-monitoring of blood pressure at home are important too [14]. Treatment compliance must be closely monitored, but it is very difficult. The major problem is the lack of persistence of the prescribed regimens. Patients should be specifically asked how successful they are in taking all of their prescribed doses, including discussion of adverse effects and dosing inconvenience. Family members will often provide more objective assessments of a patient's adherence, but such input should generally be in the presence of the patient. Direct observation of therapy is the most accurate method but is impractical for chronic diseases. Methods such as self-reporting or pillbox counting are convenient; however, it is easy to manipulate them. The medication event monitoring system (MEMS) is a practical improvement, since it records the exact time and date of opening the pillbox and it electronically stores this information in the computer (later access and control is possible). Such devices seem to be the most reliable for monitoring patients to improve their adherence. Blood or urine measurements of drug levels or biologic markers are expensive and may falsely suggest adherence in patients who take their medications only around the time of their clinic visit or white-coat adherence. In routine clinical practice, it is too expensive and not available outside reference centers [14].

5.3. Multidrug therapy

Therapy is not easily applicable to daily clinical practice. Resistant hypertension is defined as uncontrolled blood pressure on office measurements, confirmed by out-of-office measurements and the concurrent use of three antihypertensive agents including a thiazide diuretic, a renin-angiotensin system blocker (converting enzyme inhibitors (ACE) or angiotensin II receptor blockers (ARB)), and long-acting calcium channel blocker, for at least 4 weeks, at optimal doses [21]. It is important to choose combination of antihypertensive medication in fixed doses to control blood pressure. Some antihypertensive medications have advantage to show improvement of arterial elasticity by measuring central blood pressure and pulse wave velocity, with alleviation of insulin resistance and inflammation. Multidrug therapy includes adding a mineralocorticoid receptor antagonist (aldosterone antagonists) such as spironolactone and eplerenone. Dosage of spironolactone or eplerenone is 12.5–25 mg/day. Both drugs are effective for resistant hypertension but have sexual side effects and can lead to hyperkalemia especially in patients with diabetes and chronic kidney disease [24]. If adverse effects occur, or in a case of a nonresponse, a β-blocker, an α-blocker, or a centrally acting antihypertensive drug should be prescribed. General clinical examination and 24-h blood pressure monitoring have to be performed in all patients at baseline and after minimum 4 weeks of therapy to confirm resistant hypertension. In the case of failure to control blood pressure with antihypertensive multimodal regiment, with a nasal continuous positive airway pressure

ventilation in patients with obstructive sleep apnea of moderate to severe degree and resistant hypertension, renal sympathetic denervation or baroreceptor activation therapy may create a novel pathway of blood pressure control in true or proven resistant hypertension.

5.4. Device therapies for resistant hypertension

The sympathetic nervous system is very important and a forgotten pathway in hypertension treatment. It is very uncommon than in national and international society, guidelines for hypertension typically put antiadrenergic drugs to the fourth of fifth place. Many of the procedures/devices target the sympathetic nervous system and effectively and safely lower blood pressure in patients with resistant hypertension [24]. New device therapy can give additional control of true resistant hypertension. Renal sympathetic denervation, baroreceptor activation therapy, and continuous positive airway pressure were developed to interrupting the cardiovascular disease continuum, the leading cause of death globally.

5.4.1. Catheter-based renal denervation

Renal sympathetic denervation delivers energy to the renal nerves to help control blood pressure. Renal sympathetic denervation uses ablation of the renal sympathetic nerves with a radiofrequency-emitting catheter inserted percutaneously through the femur into the lumen of both renal arteries. Renal sympathetic denervation causes moderately severe abdominal pain during delivery of energy due to stimulation of the renal sensory nerves before ablation. During the procedures the use of opiates and sedatives is important to control pain. The procedure reduces sympathetic outflow from the brain which is evident in lowering of noradrenalin on plasma and in reduction of sympathetic nerve traffic to the skeletal muscle vasculature [24]. Many observational studies have shown that renal sympathetic denervation is a safe method of reducing office blood pressure in patients with resistant hypertension. Renal sympathetic denervation showed an additional positive effect on blood glucose metabolism, obstructive sleep apnea, and signs of hypertensive end organ damage [9]. The reason for the rapid introduction of renal sympathetic denervation in the therapy of resistant hypertension was the reported high efficiency and safety of the procedure [2, 10]. The effectiveness was demonstrated in the studies Symplicity HTN-1 and HTN-2 and in the EnligHTN-1 Study, by using special radiofrequency ablation catheters [10, 11]. Renal sympathetic denervation, according to the results of different trials, including Symplicity HTN-3, seems to be safe, and procedure-related complications of catheter-based renal sympathetic denervation were rare [11, 12]. Symplicity HTN-3 study did not show differences in systolic blood pressure reduction between treatment and control groups, but in the context of the study characteristics and the way it was conducted, there were several concerns about inexperienced doctors in the field of renal sympathetic denervation, the study population, and the medical treatment. Patients with diabetes and/or chronic kidney disease have sympathetic nervous system hyperactivation that leads to fluid overload, aggravation of hypertension, and further deterioration and loss of renal function. It has been demonstrated that renal sympathetic denervation is associated with stabile kidney function in those patients [11, 12]. Future focus is on long-term results of renal sympathetic denervation.

5.4.2. Baroreceptor activation therapy

Baropacing or baroreceptor activation therapy can be applied in patients with treatment-resistant hypertension. When baroreceptors sense an increase in carotid transmural pressure, they respond by inhibiting sympathetic and stimulating parasympathetic centers in the brainstem [13]. So any increase in blood pressure will return to its initial level. Most studies on baropacing took only office blood pressure as criterion for efficacy, but only one study in which the effect on 24-h was assessed showed that blood pressure had fallen by 8/5 mmHg after 6 months [13].

5.4.3. Continuous positive airway pressure

Nasal continuous positive airway pressure ventilation is considered the treatment for obstructive sleep apnea of moderate to severe degree [25]. The effects of continuous positive airway pressure on blood pressure levels have been shown to be variable, but in some subgroups of patients, those with severe obstructive sleep apnea or/and with resistant hypertension, more substantial effects of continuous positive airway pressure have been reported [24].

6. Discussion

Hypertension is the most prevalent risk factor for cardiovascular disease and death all around the world [19]. Physical activity has to be as part of our lives that is beneficial and it is a low-cost preventive strategy [24]. Lifestyle changes include weight loss, ingestion of a high-fiber, low-fat, low-salt diet, and moderation of alcohol intake. Good blood pressure control lowers risk for cardiovascular events. Despite the available pharmacological antihypertensive therapy, about 50% of patients show suboptimal control. Resistant hypertension patients often have comorbid cardiorenovascular conditions, such as heart failure, atrial fibrillation, or chronic kidney disease [20]. Hypertensive disease of the heart, blood vessels, brain (especially vascular dementia), and kidney is frequently found in patients with RH. The diagnosis of hypertension and treatment are based usually on daytime clinic blood pressure measurements. Evidence is that the asleep blood pressure better predicts cardiovascular events than the awake or 24-h blood pressure mean. The comparative outcomes in resistant hypertension deserve better understanding, and results from the Global SYMPLICITY registry (real life) showed that renal sympathetic denervation may provide an additional treatment option to reduce blood pressure in resistant hypertension patients with obstructive sleep apnea [26]. New data show that renal sympathetic denervation, by modulating the sympathetic system activation, could have an additional beneficial effect on blood pressure variability. The level of blood pressure is very important, but pattern of fluctuation of blood pressure within 24 h or variability from day to years is related to cardiorenovascular morbidity and mortality, independently of comorbidities [27].

It is important to keep the regimens for the resistant hypertension management as simple as possible. It means not only for blood pressure management but all concomitant comorbidities.

Screening and management of multisite artery disease is very important in diagnostic algorithm of resistant hypertension. In terms of costs, there is no question pharmacoeconomically that effective blood pressure control in resistant hypertension with drugs and new innovative device therapies is cheaper than treating the consequences of hypertensive target organ damage [28]. To assess drug adherence of patients with resistant hypertension in the future, an analytical method is developed in the Netherlands. Ultra-performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) is being used for validation of eight frequently prescribed antihypertensive drugs from four classes and their active metabolites in plasma. It includes enalapril and perindopril as angiotensin-converting enzyme inhibitors and enalaprilat and perindoprilat (their active metabolites), as well as angiotensin II receptor blockers losartan. Furthermore, UPLC-MS/MS includes active metabolite losartan carboxylic acid and valsartan, nifedipine, and calcium channel blockers amlodipine and diuretics (hydrochlorothiazide and spironolactone with the active metabolite canrenone) [29]. Resistant hypertension should not be considered as a synonym for uncontrolled hypertension. The latter covers all patients with hypertension: (a) whose lacking blood pressure control is not undergoing therapy, (b) who had an inadequate therapy, (c) those hypertensive patients with poor compliance, (d) those with secondary hypertension, and (e) those who are truly resistant to therapeutic treatment. Even though the definition of resistant hypertension is inconsistent regarding the number of necessary antihypertensive drugs, it is as a concept directed toward identifying the patients with high risk of target organ damage, reversible causes for hypertension and/or patients who will use special diagnostic and therapeutic options due to permanently high level blood pressure [30]. Therapeutic restoration of normal physiologic blood pressure reduction during nighttime sleep (circadian variation) is the most significant independent predictor of decreased cardiorenovascular risk and the basis for the chronotherapy [30]. Although chronotherapy is not uniformly recommended in the treatment of resistant hypertension, it is a cost-effective strategy for reducing cardiovascular risk.

7. Conclusions

Due to higher cardiovascular risk, resistant hypertension is serious and requires special diagnosis and treatment of multidisciplinary team of hypertension specialist, nephrologist, interventional cardiologist or radiologist, and nurse.

It is important that patients understand the rationale for good adherence to antihypertensive therapy. Poor adherence is a major cause of lack of blood pressure control, and it can be misleading in further diagnostics and treatment with detection of drugs in blood and/or urine. New devices were developed to interrupting the cardiovascular disease continuum, the leading cause of death globally. New devices for hypertension should only be prescribed by a specialist hypertension clinic. Recently published interim result from the SPYRAL HTN-OFF MED study showed that more intensive approach to ablating renal nerves that the one used in the failed SYMPLICITY HTN-3 trial can reduce blood pressure in a patient with untreated mild to moderate hypertension. It provides biological proof of principle for the efficacy of renal sympathetic denervation [31].

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Chapter 9

Treatment of Resistant Hypertension: An Update in Device Therapy

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Additional information is available at the end of the chapter

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Abstract

Hypertension is the most prevalent cardiac risk factor. In the United some estimates show 60% of 60-year-olds, 70% of 70-year-olds, an 80% of 80-year-olds being hypertensive. Often, blood pressure becomes resistant or refractory. Device therapy represents a new approach to treating this disease. The best studied of these nonpharmacologic approaches to resistant/refractory hypertension include renal denervation, carotid sinus stimulators, and central arteriovenous fistula placement. This chapter will focus on novel device therapy and literature review of its use in clinical trials.

Keywords: resistant hypertension, renal denervation, central arteriovenous anastomosis, carotid sinus baroreceptor electrical stimulators

1. Introduction: Resistant hypertension and renal denervation

Resistant hypertension, defined as blood pressure greater than 140/90 despite the use of optimal doses of three blood pressure-lowering medications, including a diuretic, is a growing epidemic. Today, approximately 86 million Americans and 1.4 billion people worldwide suffer from hypertension, and of these, 8–12% are estimated to have resistant hypertension [1, 2]. The sequelae of resistant hypertension include significant cardiovascular morbidity and mortality as well as significant healthcare costs. Medication non-adherence is among the foremost important factors in the propagation of hypertension, and may affect up to 50% of patients, obscuring the true prevalence of resistant hypertension [3]. Nevertheless, as the problem of hypertension grows, so do the various modalities of its treatment. Here, we review the efficacy and future of device based therapy in the treatment of resistant hypertension.

Surgical intervention in the management of hypertension originated over 60 years ago, when significant decreases in blood pressure were noted following surgical lumbar sympathectomy [4]. Significant adverse effects including orthostatic hypotension, impotence and bowel and bladder dysfunction were common, thus when oral blood pressure-lowering agents became available just a few years later, such surgical techniques essentially ceased. Over the last decade, there has, once again been a resurgence of device-based therapies for the treatment of resistant hypertension, part due to the first proof-of-principle trial, the SYMPLICITY-HTN-1 trial. Renal denervation in particular has been the most-studied device-based therapy and continues to garner much attention with an ever-growing body of evidence, both critical of, and in support of its use. Other modalities such carotid sinus baroreceptor electrical stimulators and central arteriovenous anastamoses have shown some promise but neither therapy has found a niche and remained unapproved by the Food and Drug Administration in the United States. Because of their novel approach to hypertension, this chapter will review these modalities and their associated clinical trials data.

2. The theory behind renal denervation

Increased sympathetic nervous system (SNS) activity may partially underlie both high blood pressure and hypertension maintenance [5, 6]. Although the SNS innervates the entire human body, hypertensive patients do not experience increased SNS activity in all organs. By detecting SNS activity through measurements of norepinephrine release, SNS over-activity is detected in renal, cerebral and cardiac circulations but not in the pulmonary or splanchnic systems [7]. Within the kidneys, outflow from the efferent sympathetic nerves stimulates renin release and increased tubular sodium reabsorption and as a result, increases blood pressure [8]. The afferent sympathetic outflow from kidneys can contribute to neurogenic hypertension via increased total peripheral resistance, including increased sympathetic nerve activity to the heart and kidneys, all of which work to increase blood pressure [8]. The specific targeting of organs, such as the kidneys, is therefore a logical approach in mitigating SNS hyperactivity.

Renal denervation involves accessing the renal arteries via the femoral artery and delivery of either radiofrequency or ultrasound energy, resulting in frictional heating of the arterial wall (see **Figure 1**) [9]. The aim of this is to destroy a significant portion of the renal sympathetic nerves, which are believed to lie closely to the renal artery, usually within the adventitia [10]. In rat models of renal denervation, renal norepinephrine levels were measured following denervation and were found to be significantly decreased, which correlated with significant delays in onset of hypertension in spontaneously hypertensive rats [11]. Swine studies later performed also demonstrated that consistent reduction in norepinephrine could be achieved and that targeted treatment of the renal artery branches, distal segment of the main renal artery or a combination of the two resulted in the most dramatic reductions in blood pressure [12]. Various methods have been used to assess the efficacy of renal denervation in humans. The most common method, the renal norepinephrine spillover method, measures the release of norepinephrine from the renal sympathetic nerves bilaterally via isotope dilution [13, 14]. Decreased norepinephrine spillover would indicate successful renal denervation. The amount by which norepinephrine should decrease per renal nerve denervation is, however, unknown.

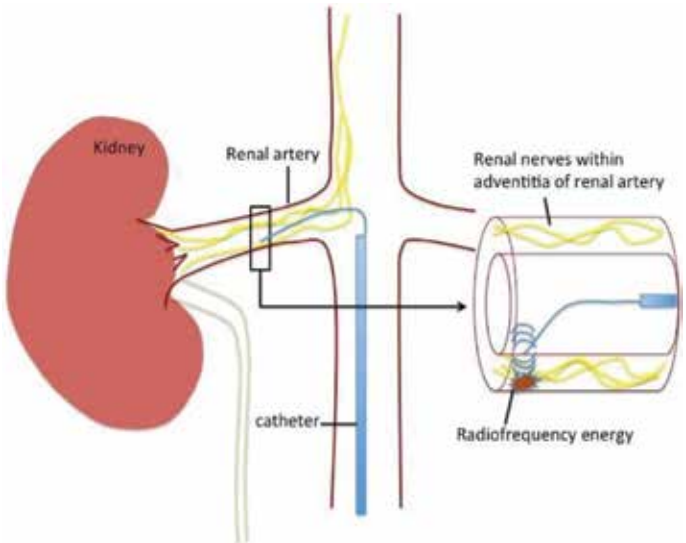

Figure 1. Schematic of renal nerve denervation.

3. Current evidence behind renal denervation

The Symplicity-HTN-1 trial thrust renal denervation into the spotlight. The patient population in this study had resistant hypertension, defined as systolic in-office blood pressure >160 mm Hg despite the use of three antihypertensive agents including one diuretic. In this open-label trial, the patient population was subject to renal denervation via a percutaneous radiofrequency catheter. The study investigators achieved the primary endpoint of sustained decrease in systolic and diastolic blood pressures at 1, 3, 6, 9 months and 12 months out from renal denervation, in contrast to the untreated control group (n = 5), who showed no significant change in blood pressure [15]. The investigators measured the renal norepinephrine spillover in a subset of patients (n = 10) and saw a modest but significant reduction of 47%. This study showed that renal denervation was safe and tolerated well among patients and was further backed up by a 3-year follow up study by the same group showing persistent reduction in blood pressure as well as continued safety following renal denervation in the Symplicity-HTN-1 trial [16].

Following up this success, the same study investigators constructed an open-label randomized trial, Symplicity-HTN-2, which randomized 106 patients to receive renal denervation via a percutaneous radiofrequency catheter or to continue their previous treatment regimen. Again, the investigators showed they achieved the primary endpoint, a significant decrease in office-based blood pressure at 6-month follow-up versus no significant change in blood pressure in the control group at 6-month follow-up [17]. A 36 month follow-up study conducted by the same investigators again showed sustained reduction in blood pressure and good safety profile in patients who had undergone renal denervation in the Symplicity-HTN-2 trial [18].

The major criticism of the Symplicity-HTN-2 trial and other major renal denervation trials was a lack of blinding and appropriate powering, thus the Symplicity-HTN-3 trial was designed as a randomized, single-blind, sham-controlled trial. Following randomization of 535 patients, investigators assessed the primary outcome of in-office blood pressure and secondary outcome of 24-hour ambulatory blood pressure. This trial however, failed to show a significant difference in blood pressure at the 6-month follow-up in the experimental group compared with the sham-procedure group [19]. Prior to completion of this trial, renal denervation had gained enough momentum to be on track for approval by the Unites States Food and Drug Administration and was to be used in an even larger international trial, the Symplicty-HTN-4 trial. However, following the negative results of the Symplicity-HTN-3 trial, the Symplicity-HTN-4 trial as well as FDA approval, were put on hold.

There are many possible explanations for why the Symplicity-HTN-3 trial did not reach its primary outcome. Patel et al., highlight several important factors distinguishing Symplicity-HTN-3 from earlier trials. First, the original trials lacked ambulatory blood pressure monitoring and may have misidentified white-coat-hypertension as resistant hypertension. The experience of the probe operators was brought into question and that there was uncertainty regarding whether the procedures were technically successful, as there was no objective measurements made (i.e., norepinephrine spillover measurement) following renal denervation. Finally, the sham-control group in Symplicity-HTN-3 had a larger drop in blood pressure than the control group and that had it not been for this, the trial would have actually met its primary outcome. They note the important finding that placebo effects do wear off over time, and that it may have been telling to monitor blood pressure beyond 6 months following the renal denervation procedure [20]. Renal denervation has not been abandoned but continues to undergo fine tuning.

4. Central arteriovenous fistula formation

Several physiologic mechanisms have been suggested to allow blood pressure reduction in patients with arterial hypertension who undergo arteriovenous fistula formation. Burchell et al. outlined these potential mechanisms in great detail. The primary mechanisms are likely a reduction in total systemic vascular resistance and a reduction of effective arterial volume [21, 22]. The reduction in systemic vascular resistance (SVR) likely occurs given the creation of two parallel circuits leading to the total resistance being less than the value of the lowest resistance circuit. Furthermore, by allowing arterial blood to flow preferentially through the low resistance anastomosis, arterial blood volume and thus afterload are reduced leading to decreased cardiac work with an associated increased cardiac output [21]. Multiple studies evaluating the resultant effects of arteriovenous fistula (AVF) formation support a reduction in SVR and arterial volume with an increase in cardiac output [23]. The resulting cardiopulmonary response to AVF formation is unclear, however, multiple mechanisms may play a role. Some of these responses even represent conflicting physiologic mechanisms. Cardiac reflexes may include increased right atrial pressure and subsequent atrial natriuretic peptide release leading to vasodilation and increased renal blood flow, the Bainbridge reflex leading to diuresis

and tachycardia, activation of vagal mechanoreceptors leading to bradycardia and inhibition of sympathetic activity, and coronary baroreceptors leading to decreased SVR. Pulmonary reflexes may include increased pulmonary arterial oxygen content leading to pulmonary arterial vasodilation, and activation of pulmonary arterial baroreceptors triggering sympathetic activity leading to tachycardia and increased peripheral arterial pressure [21].

Renal chemoreceptors may also play a role in reducing sympathetic activity due to increased afferent arterial oxygen delivery. This mechanism can be likened to those affected by renal artery denervation and are described elsewhere [21].

Due to the coexistence of multiple pathways, studies are unclear as to the effect of AVF formation on arterial oxygen content and delivery. It has been suggested that increased arterial oxygen content would at least partially offset or in some ways suppress already active or secondarily activated peripheral and central pathways of sympathoexcitation. Suggested pathways include the renin-angiotensin-aldosterone pathway, the Cushing response, and other less specific peripheral chemoreceptors [21].

Initially developed for treatment of patients with chronic obstructive pulmonary disease (COPD) , the ROX coupler system is a nitinol device that is placed forming a 4 mm diameter anastomosis between the external iliac vein and artery. Early prospective data suggested improvement in office and 24-hour arterial blood pressures after AVF creation in patients with both COPD and

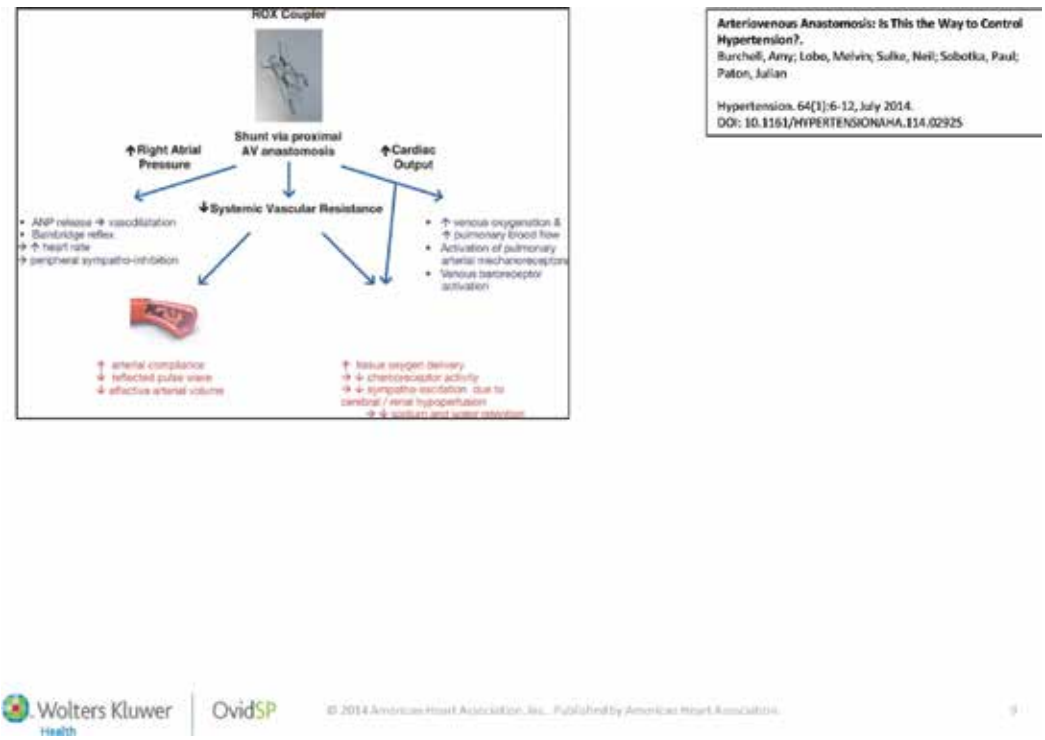

Figure 2. Schematic of the ROX Coupler.

hypertension [22, 24]. In 2015, the ROX CONTROL HTN study, a multi-center randomized controlled trial compared current treatment to ROX coupler placement plus current treatment via intention-to-treat analysis. Eighty-three subjects with resistant hypertension were randomized. Those in the ROX coupler group experienced a statistically significant decrease in both mean systolic blood pressure and mean systolic 24 hour ambulatory blood pressure over 6 months. ROX coupler patients were given graduated surgical compression stockings on the treated limb for at least 2 weeks post-placement. The most common adverse effect was symptomatic venous stenosis occurring in 12 (29%) of the 42 patients treated with coupler placement. All 12 patients were subsequently managed with self-inflating venous stents with resolution of symptoms. No patients in the coupler arm were admitted for hypertensive crisis while 3 (8%) of the 39 in the control arm were [25]. As of 2017, multiple randomized trials involving the ROX COUPLER are either recruiting or are underway. **Figure 2** illustrates the Rox-Coupler system [21].

5. Carotid sinus baroreceptor electrical stimulators

Recognizing that as hypertension progresses, changes in the Sympathetic Nervous System occur and can contribute to congestive heart failure and blood pressure. Reduced parasympathetic and elevated sympathetic tone lead to increased peripheral vascular resistance, lower renal blood flow, salt retention, and vascular remodeling. In 2011 the Rheos Pivotal Trial addressed the use of Baroflex Activation Therapy (BAT). This surgically implantable device (Rheos System, CVRx, Inc., Minneapolis, Minnesota) was created to administer BAT via electrical stimulation of the carotid baroreceptors. The device, placed subcutaneously, consists of a pulse stimulation generator on the anterior chest wall with bilateral electrodes tunneled to each carotid sinus. It delivers an exogenous source of energy to the carotid baroreceptors, interpreted in the central medulla as a rise in BP. The brain then sends sympathoinhibitory signals to the blood vessels, heart, and kidneys resulting in a reduction of BP [26]. **Figure 3** illustrates the BAT system [26].

The 2011 Rheos Pivotal trial enrolled 265 subjects. Each had the device surgically implanted but only half had it activated at first. After 6 months all subjects had the device activated. While the trial did show a significant change in subjects whose blood pressure fell below 140/90 mm Hg, it failed to show a significant drop in systolic blood pressure. Furthermore, several safety issues arose and temper enthusiasm for this device moving forward. The device remains unapproved by the Food and Drug Administration [27].

Recognizing that both BAT and Renal Denervation modulate sympathetic signals, Wallbach et al. identified 28 subjects who had previously undergone renal denervation and enrolled them in a clinical trial to evaluate their collective response to BAT. Enrolled patients still had resistant hypertension at the time of BAT deployment with a mean systolic blood pressure (SBP) >180 mm Hg. 68% of subjects had >10 mm Hg fall in SBP after BAT. SBP dropped from 182 down to 163 mm Hg. Both findings were statistically significant. Although renal function did not differ, interestingly, albuminuria fell significantly as well. This suggests that those who “fail” one form of device therapy may benefit from a different approach [28].

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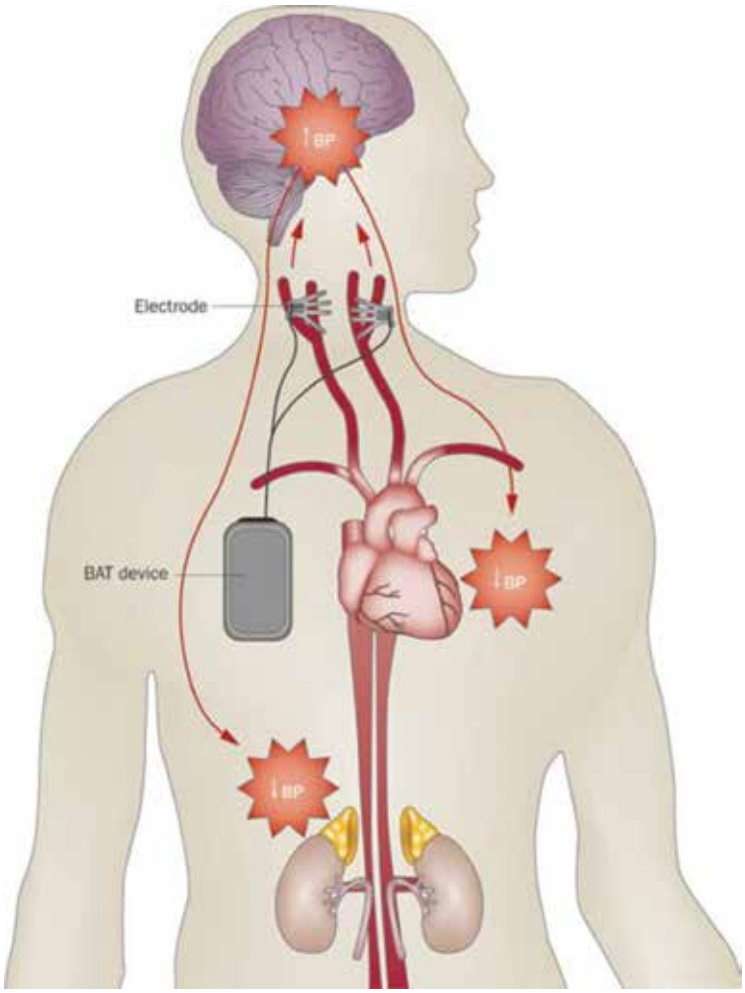

Figure 3. Schematic of carotid sinus baroreceptor electrical stimulators.

In 2016 Wallbach et al. prospectively evaluated subjects who had undergone BAT placement and performed 24 hour ambulatory blood pressure monitoring (ABPM) before device implantation and 6 months after it. His group was able to show a statistically significant drop in systolic and diastolic pressures (8 and 5 mm Hg) as well as a drop in blood pressure medications (6.5–6) follow device deployment [29].

6. Optimal modality for blood pressure monitoring

The decision to look at 24 hour ABPM is interesting given the debate regarding best practices in terms of obtaining the most accurate and reliable blood pressure readings. Bakris et al.

commented on this. Most cardiovascular outcome trials, to date, have used either auscultatory or automatic oscillometric methods of seated BP measurement performed shortly after the patient's arrival for a visit, with similar methods currently used in most clinical practices [30].

Giorgini et al. point out that in many hypertension clinical trials there is tremendous variability in the methodology from one trial to the next. For example, the actual practitioner measuring the blood pressure, the temporal relationship to the last medication dosage, the number of readings taken to provide a documented blood pressure, resting time between readings, and the device used. It is this lack of uniform procedures in such outcome studies that continue to make evidence-based guidelines difficult to determine a single best practice for blood pressure measurement that improves the ability to compare one trial to the next [31]. For now it would appear that so long as the method chosen is sound and reproducible in multiple centers, that may suffice.

7. Conclusions

Resistant and refractory hypertension often lead practitioners to consider device therapy. Thus far, the results from major trials in device therapy have been disappointing. While there was much hope following the initial SYMPLICTY trials, when this procedure/device therapy was applied to a larger cohort, the results were no different statistically. There is some debate however that the denervating instrument in earlier trials was not sophisticated enough to complete the process of denervation. Newer probes are now available renewing optimism in this procedure. The ROX Coupler caused significant venous stenosis, lacks longer-term follow-up data, and BAT while effective to some extent, was also fraught with significant side effects limiting applicability. Those with resistant hypertension who fail one form of device therapy may be considered for an alternative provided it is available. We believe there may be some hope for device therapy, particularly in the field of renal denervation, and studies are underway to address this.

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Since the discovery of blood pressure by Stephen Hales in 1733, scientific interest in blood pressure regulation, particularly in hypertensive population, has not lost its popularity. The importance of the interactive effects of blood pressure shifts in different clinical conditions is well understood. We know many contributing factors regulate the pressure of the blood within the arteries. However, crucial blood pressure control and the exact mechanisms involved are still under debate. The present book aims to cover blood pressure from its measurement to various factors of its control with valuable contributions from different authors, in the light of contemporary data, from bench to bed.

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