HIGH BLOOD PRESSURE & PREGNANCY

AN INTRODUCTION

DR HIDAYATUL RADZIAH ISMAWI
DR MAIZURA MOHD ZAINUDIN
DR NURJASMINE AIDA JAMANI

HIGH BLOOD PRESSURE & PREGNANCY

AN INTRODUCTION

BY:
DR HIDAYATUL RADZIAH ISMAWI
DR MAIZURA ZAINUDIN
DR NURJASMINE AIDA JAMANI

EDITOR:
DR HIDAYATUL RADZIAH ISMAWI

DISCLAIMER

THIS E-BOOK IS WRITTEN BY HIDAYATUL RADZIAH ISMAWI, DR MAIZURA MOHD ZAINUDIN, DR NURJASMINE AIDA JAMANI, KUANTAN, PAHANG AND PUBLISHED BY THE MALAYSIAN INTEGRATED MEDICAL PROFESSIONALS ASSOCIATION, KOTA KINABALU, SABAH. THE AUTHOR IS NOT RESPONSIBLE FOR THE SUITABILITY OF CONTENTS TO ALL READERS.

Published by:
Malaysian Integrated Medical Professionals Association (MIMPA)
Kota Kinabalu, Sabah

e ISBN 978-629-96678-2-7
9 7 8 6 2 9 9 6 6 7 8 2 7

PREFACE

This e-book was published to embrace the concept of open access of knowledge and sustainability.

Hypertension is the leading chronic cardiovascular disease (CVD) affecting 5.8 million Malaysians. The prevalence of hypertensive disorders of pregnancy (HDP) in Malaysia is approximately 23.3 per 1000 live births. HDP can cause both maternal and foetal morbidity and mortality. It is also an independent risk factor of CVD with endothelial dysfunction postulated as the main pathophysiology.

ACKNOWLEDGEMENTS

In the name of Allah the most Gracious and the most Merciful, we would like to say Alhamdulillah for His Mercy and His Guidance throughout the time it required us complete this e-book. We pray that whatever knowledge and experience He continues to allows us to pursue will be of value and benefit to others.

AUTHORS

Asst. Prof. Dr Hidayatul Radziah Ismawi

MBBS, IIUM
PhD (Medical Sciences), IIUM
Lecturer, Kulliyyah of Medicine, IIUM

Asst. Prof. Dr Maizura Mohd Zainudin

MBBS, IIUM
PhD (Medical Sciences), UKM
Lecturer, Kulliyyah of Medicine, IIUM

Assoc. Prof. Dr Nurjasmine Aida Jamani

MD (UKM)
M.Med (Fam Med), UKM
Lecturer, Kulliyyah of Medicine, IIUM

BLOOD PRESSURE & HYPERTENSION

PHYSIOLOGY OF BLOOD PRESSURE

BP is the measurement of the pressure of the blood as it pushes against the artery wall. It peaks when the heart muscle contracts and pumps blood, during a cycle called systole. When the heart relaxes, the pressure falls and the heart refills with blood, during a cycle called diastole (Hall & Guyton, 2011). Adequate BP is essential for organ function. Therefore, BP control is essentially the sum of the control of blood flow to any given tissue in proportion to its individual metabolic needs.

Factors Affecting Blood Pressure

Blood pressure (BP) is determined by cardiac output (CO) and total peripheral resistance (TPR) or systemic vessel resistance (SVR).

$$\mathbf{BP = CO \times TPR}$$

The blood volume that is pumped out by the heart in a single minute is the CO. It is determined by the heart rate (HR) and stroke volume (SV), therefore changes in HR or SV will affect CO. Regulation of CO involves intrinsic mechanisms of the heart, hormones and the autonomic nervous system (ANS).

CO = SV × HR

The volume of blood ejected by each ventricle during each contraction is the SV and is determined by three main factors. The factors are:

- end diastolic volume (EDV) also known as preload
- heart contractility, which is determined by the sympathetic stimulation of the heart
- the amount of resistance (TPR) the heart has to encounter when it pumps the blood out, or the afterload

When EDV and heart contractility increases, there is an increase in SV. EDV is affected by venous return, which is in turn affected by cardiac suction effect and central venous pressure (CVP). CVP is the pressure of blood in the thoracic superior cava and inferior vena cava as they enter the heart. Additionally, EDV affects the heart contractility based on the Frank-Starling mechanism. As EDV increases, the ventricular sarcomeres stretches resulting in stronger ventricular contraction (Hall & Guyton, 2011).

CVP is determined by blood volume, peripheral venous tone, skeletal muscle activity (skeletal muscle pump) and respiratory activity (respiratory pump). Blood volume, is affected by the renin-angiotensin-aldosterone system (RAAS), vasopressin and tissue fluid volume (Klabunde, 2011). Aldosterone, in RAAS, reabsorbs sodium and water from the distal tubules and collecting ducts of the kidney, whereas vasopressin increases water

reabsorption in the collecting ducts of the kidney (Sherwood, 2010).

Global neural control of arterial hypertension is essentially through the sympathetic nervous system (SNS). Stimulation of the sympathetic nervous system (SNS) also causes venoconstriction by binding of adrenaline and noradrenaline (NA) to α1 adrenagic receptors, which increases the pressure gradient and facilitates venous return as two-thirds of total blood volume is placed within the capacitance vessels, namely the veins (Hall et al., 2012; Jacob et al., 2011).

The arterial pressure against which the ventricles pump is known as the afterload. During ventricular systole, the pressure in the ventricles must exceed the pressure in the aorta or the pulmonary artery in order to open the semilunar valves. Therefore, higher resistance or afterload will result in lower SV (Hall & Guyton, 2011).

Moreover, the HR, which is generated by the sinoatrial (SA) node; and heart contractility depends on the relative balance of parasympathetic and sympathetic activity. Sympathetic activity occurs from stimulation by binding β1 adrenergic receptors; while parasympathetic activity decreases HR and contractility by means of acetylcholine via muscarinic receptors (Barret et al., 2012).

Another factor affecting the mean arterial pressure (MAP) is TPR. TPR is the resistance of the entire systemic vasculature in the body. The major determinants of TPR are blood viscosity and arteriolar diameter, with arteriolar diameter being the more important factor of the two.

Higher blood viscosity, as seen in polycythaemic patients, will cause an increase in the resistance to blood flow, subsequently increasing the TPR. Meanwhile, a decrease in arteriolar diameter caused by smooth muscle contraction will increase arteriolar resistance. Conversely, an increase in arteriolar diameter caused by

smooth muscle relaxation will decrease arteriolar resistance.

Both local metabolites control mechanism and extrinsic mechanism (sympathetic activity stimulation and hormones) regulate arteriolar diameter. The arteriolar smooth muscle possesses a vascular tone, namely a normal state of partial constriction. This vascular tone establishes a baseline of arteriolar resistance. There are two main factors that are responsible for this action. Firstly, myogenic activity; when the arteriolar smooth muscle membrane potential fluctuates independent of any neural or hormonal influences. This leads to independent contractile activity. The second factor is the continual release of NA by sympathetic fibres that supply most arterioles, which further enhances vascular tone (Yokoyama et al., 2015).

Local (intrinsic) control and extrinsic control are the main mechanisms that influence the arteriolar contractile activity and hence, their diameter. Contractility of the arteriole can be regulated by the extrinsic control mechanism via ANS, primarily by the sympathetic nerves and by the circulating hormones. There is no significant parasympathetic innervation to arterioles with the exception of the arterioles of the male penis and female clitoris (where a myriad of parasympathetic vasodilators supply the arterioles). In other parts of the body, increased sympathetic activity causes generalised arteriolar vasoconstriction, while decreased sympathetic activity instead of increased parasympathetic activity, produces generalised arteriolar vasodilation. Through sympathetic nerve endings, the release of NA that binds to α1 adrenergic receptor will lead to vasoconstriction. Arterioles in the brain are the only ones that do not have the α1 receptors so that no vasoconstriction will occur because blood flow to the brain must remain constant to meet the brain's continual need for oxygen.

The hormones involved in the hormonal regulation of the arteriolar diameter are adrenal medullary hormones (adrenaline and NA), which generally reinforce the sympathetic nervous system in most organs; and the vasopressin and angiotensin II (ANG II), which are crucial in controlling fluid balance. NA released by the adrenal medulla combines with the same α1 receptors, to produce generalised vasoconstriction. While the release of adrenaline that binds to α1 receptor will have the same effect as NA has, the binding of adrenaline to the β2 receptor (which can be found abundantly in the arterioles of skeletal muscles and the heart) will cause arteriolar vasodilation. Adrenaline has a much greater affinity towards the β2 receptors (Hübner et al., 2015; Yokoyama et al., 2015).

Vasopressin and ANG II are other hormones that extrinsically influence arteriolar tone and hence blood flow, play important roles in maintaining water balance while ANG II is crucial in regulating the body salt balance. Both are

potent vasoconstrictors and especially important during haemorrhage (Wang et al., 2010).

Local arteriolar adjustments can override the sympathetic constrictor effect in order to ensure that MAP can still be maintained. Furthermore, this guarantees an adequate blood flow to the organs, especially the crucial organs such as the brain or organs that really need additional blood such as active muscles; including the heart muscle. Local control mechanisms of blood flow can be both chemically and physically influenced. The local chemical influences include local metabolic changes and histamine (HA) release, correspondingly the local physical influences are local application of cold or heat, chemical response to shear stress and myogenic response to stress (Hall & Guyton, 2011).

The most important local chemical influences on arteriolar smooth muscle are local metabolic changes. Table 2.1 lists these local chemical changes and their net effect.

The most important physiological physical influences on arteriolar smooth muscle are the chemically mediated response to shear stress and the myogenic response to shear stress (Sherwood, 2010). Cold application produces vasoconstriction, while heat application will cause a localized arteriolar vasodilation (Barret et al., 2012).

An increase in shear stress will cause NO to be released by the endothelial cells (Barret et al., 2012, Hall & Guyton, 2011, Rautureau & Schiffrin, 2013). This will lead to vasodilation, causing a reduction of the shear stress resulting from increased vessel diameter. An increase in blood volume as well as an increase in MAP will drive more blood forward into the arterioles and cause the arteriolar smooth muscles to be passively stretched. The arteriolar smooth muscle responds by increasing its tone through vasoconstriction myogenically. Conversely, a reduction in arteriolar stretching, which can be caused by arteriolar occlusion that blocks blood flow into the arterioles will cause a reduction in

myogenic vessel tone by promoting vasodilation (Hall & Guyton, 2011).

Table 2.1 Local chemical changes and their net effect on arteriolar smooth muscle

Chemical signal	Source	Effect
Signals related to metabolism		
Oxygen (O_2)	Delivered by arterial blood; consumed in aerobic metabolism	Vasoconstriction (Rapid metabolism depletes O_2, which causes vasodilation)
Carbon dioxide (CO_2)	Produced by aerobic metabolism	Vasodilation
Potassium ions (K^+)	Released from rapidly metabolizing cells	Vasodilation
Adenosine	Released from rapidly metabolizing cells	Vasodilation
Metabolic acids (e.g., lactic acid)	Produced by anaerobic metabolism	Vasodilation
Other Local Chemical Signals (Paracrines)		
ET-1	Endothelial cells	Vasoconstriction
NO	Endothelial cells and some parasympathetic nerve endings	Vasodilation
Thromboxane A_2 (TXA_2)	Platelets	Vasoconstriction (also increases platelet aggregation)
Prostacyclin (PGI_2)	Platelets	Vasodilation (also decreases platelet aggregation)
Histamine	Mast cells	Vasodilation (also increases capillary permeability)
Bradykinin	Globulins in blood or tissue fluid	Vasodilation (also increases capillary permeability)

(Ashina et al., 2015; Davenport et al., 2016; Hall et al., 2012; Mitchell et al., 2008)

Another important hormone that is important in BP regulation is atrial natriuretic peptide (ANP), which is secreted by the heart specifically myocardial cells, as a response to hypervolaemia. Volume expansion of circulating blood volume will cause the release of ANP when the atrial myocardial cells are stretched. It circulates in the blood and antagonizes the action of various vasoconstrictor agents and therefore, lowers BP. Along with brain natriuretic peptide (BNP), it also serves to coordinate the control of vascular tone with fluid and electrolyte homeostasis via actions on the kidney (Barret et al., 2012; MacHeret et al., 2012). Moreover, ANP inhibits the reabsorption of sodium in distal convoluted tubules, causing natriuresis and subsequent diuresis. Hence, the ECF volume is decreased and results in BP decrease. The ANP also inhibits the release of renin from the kidney, causing a decrease in ANG I and II, as well as aldosterone. This may lead to systemic vasodilation and arterial hypotension (Jacob et al., 2011).

Regulation of Blood Pressure

There are two types of regulatory mechanisms of arterial BP; the short term and long term mechanisms. Short term regulation often increases pressure within 5 to 10 seconds while for long term regulation, minutes to days are required to increase the BP. The short term mechanism (Refer Figure 2.3) is mediated by nervous control, regulating blood vessel diameter, heart rate, and contractility while the longer-term mechanism is largely mediated by hormones and kidneys by controlling the blood volume. For the short term mechanism, there are three types of reflexes reacting to a change in BP; whereas for the long term mechanism, the system involved is the RAAS (Klabunde, 2011).

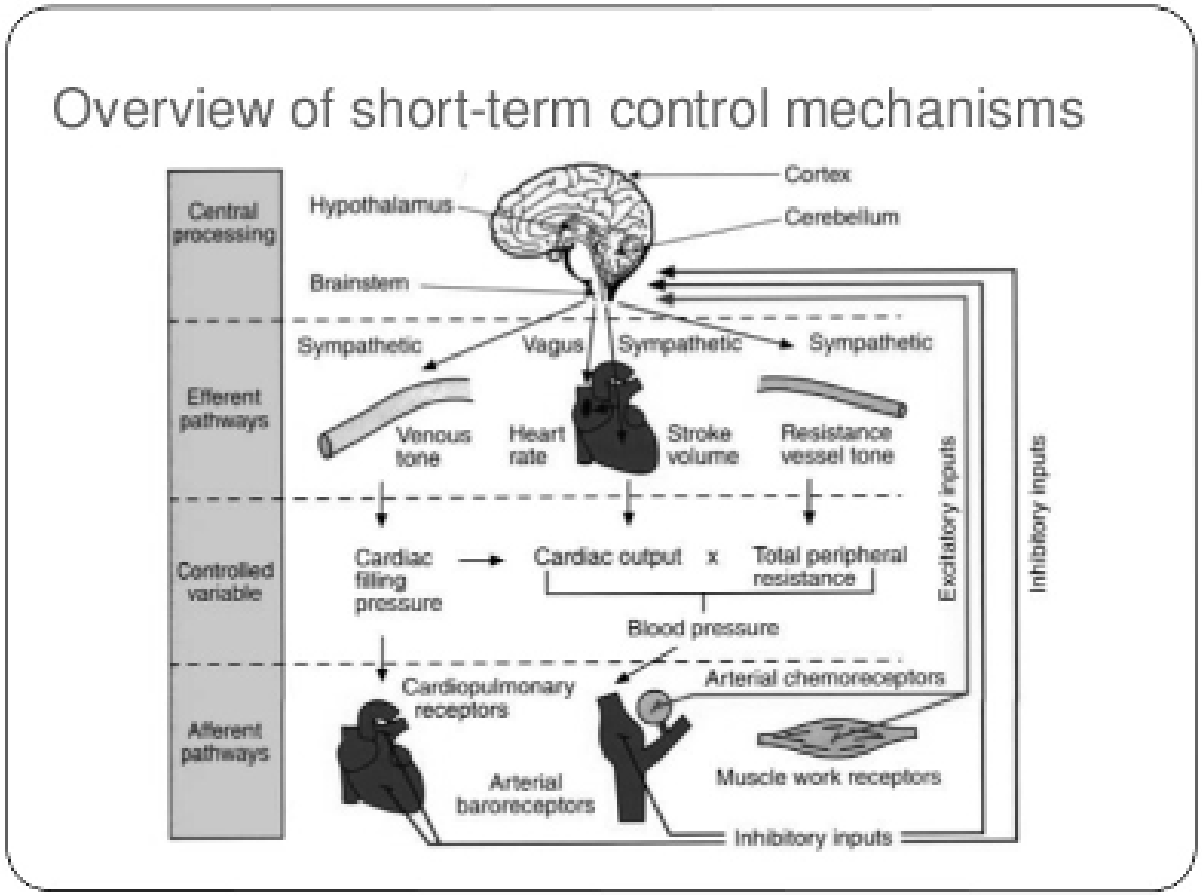

Figure 2.3 Short term mechanisms of blood pressure (BP) control (Herring & Paterson, 2018)

The three responses which are involved in the short term mechanism are the baroreceptor reflex, the chemoreceptor reflex and the central nervous system (CNS) ischaemic response. The baroreceptor reflex is the best known among the three (Wehrwein & Joyner, 2013). When MAP is increased above its normal range (more than 60 mmHg); the baroreceptors (stretch receptors), which are sensory nerve endings in

the walls of the aortic arch and carotid sinuses sense a stretch in the walls of both vessels. Impulses will be sent to the medulla oblongata to nucleus tractus solitaries (NTS). The nerve fibres in NTS project to the rostral ventrolateral medulla (RVLM) or cardio-acceleratory centre (CAC) and the cardio inhibitory centre (CIC) in the medulla, which controls the activities of the sympathetic and parasympathetic nerves respectively, through the glossopharyngeal nerve (9th cranial nerve) from the carotid sinuses and the vagus nerve (10thcranial nerve) from the aortic arch (Patton & Thibodeau, 2010).

The CIC activity is then stimulated and results in increased parasympathetic activity to the heart. Consequently, the heart rate decreased as acetylcholine released by parasympathetic nerves acts on the muscarinic receptors and impulse conduction through the AV node is decreased. As a result, cardiac output is decreased and hence the blood pressure will be decreased too (Klabunde, 2011).

Parasympathetic nerves innervate very little number of vascular beds to cause a significant effect on arteriolar resistance. Nonetheless, a concurrent decrease in sympathetic activity will cause vasodilation, causing a decrease in TPR.

Conversely, when MAP decreases below the normal range, the baroreceptors in both carotid sinuses and aortic arch decreases the firing rate. The NTS then stimulates the activity of RVLM or CAC and results in increasing sympathetic activities to the heart and blood vessels. The resultant increase in heart rate, increased impulse conduction through AV nodes, increased SV due to increased cardiac contractility and increase in TPR (caused by vasoconstriction) lead to increase in blood pressure (Klabunde, 2011).

Chemoreceptors are not powerful enough to be the only control of arterial pressure in the normal arterial pressure range since they will only be stimulated by MAP that is less than 80 mmHg.

The chemoreceptors are located at the carotid and aortic bodies and are sensitive to low oxygen as well as pH (high blood acidity or carbon dioxide). The main function of chemoreceptors is to increase respiratory activity, but it also has effects on the cardiovascular system. When the blood pressure falls below critical level (less than or equal to 80 mmHg), the blood flow will decrease and this will result in increased carbon dioxide, decreased oxygen, and hypoxia, respectively. All these local accumulation of metabolites will stimulate the chemoreceptors that will in turn stimulate the VMC or CAC which eventually leads to elevation of blood pressure (Hall & Guyton, 2011).

CNS ischaemic response is a nervous control in response to intense cerebral ischaemia. It is not one of the usual mechanisms to regulate normal blood pressure because it only plays a role when there is severe hypotension (MAP falls far below normal that is less than 60 mmHg).

When blood flow is reduced, the local metabolites accumulation will stimulate the chemoreceptors and thus the VMC or CAC will accordingly be stimulated that results in increment of the blood pressure (Hall & Guyton, 2011).

However, when the changes in arterial pressure occur slowly over a period of many hours or days, or even years, the nervous control mechanism will gradually lose the total ability to compensate the changes (Klabunde, 2011). Long term blood pressure regulatory mechanism is the integrated renal-endocrine systems that balance the body fluid and salt homeostasis with control of arterial hypertension, alters the blood pressure by controlling the blood volume. Blood volume influences the venous return, end diastolic volume, stroke volume, and cardiac output. It can be concluded that blood volume is a major determinant of arterial blood pressure since all these factors affects the MAP (Hall et al., 2012).

If blood pressure decreases below a normal range, the long term mechanism will try to increase the blood pressure by means of RAAS and antidiuretic hormone (ADH). Aldosterone will cause sodium retention while ADH will cause water to be retained. When BP decreases below a normal range, there will also be a subsequent decrease in the renal blood flow (Wang et al., 2010). When this happens, granular cells (the juxtaglomerular apparatus) secretes renin into the blood. Renin acting as an enzyme, converts inactive angiotensinogen, a plasma protein synthesized in the liver into active angiotensin I. Angiotensin I will then be converted to ANG II upon passing through the lung via pulmonary circulation (by the help of the angiotensin converting enzyme [ACE] in the lungs). These response will finally lead to the increment of the extracellular fluid (ECF) volume (Hall & Guyton, 2011).

HYPERTENSION

Prior to 1960, the general consensus among physicians was that high BP was a natural consequence of aging and not risk factor that needed to be controlled. A majority of physicians believed that BP lowering was dangerous, if not useless, despite the increasing epidemiological evidence of association of high BP with mortality increment. It was not until the late 1960s that a trial, the first Veteran Affairs Cooperative Study had provided the first strong casual evidence that BP lowering reduces the risk of death (Rahimi et al., 2015). Since then, countless numbers of studies have recognized hypertension as a major risk factor for cardiovascular and renal events such as myocardial infarction, hypertensive heart disease, heart failure, atherosclerosis, aortic aneurysm, peripheral artery disease, stroke and end-stage renal disease, and overall mortality that affects the population of all categories (Chen, 2012; Garovic et al., 2010; Pimenta & Calhoun, 2010).

In 2015, 70% of the overall total of 56 million deaths globally occurred due to NCDs with CVDs accounting for 45% (17.7 million deaths) of all the NCD deaths, beating deaths by cancer (22%), chronic respiratory disease (10%), and diabetes (4%) (World Health Organization, 2017).

A systematic analysis of population-based studies from 90 countries by Mills et al. 2016, showed that in 2010, 31.1% of the world's adults (aged 20 years or more) had hypertension (with average SBP of 140 mmHg or more, average DBP of 90 mmHg or more, or using antihypertensive medication). Malaysia is also in the same proverbial boat. Data from the NHMSs from 1996 to 2011 showed there was a rising trend in the prevalence of hypertension in adults aged 30 years or more (Naing et al., 2016).

Hypertension has previously been defined as a sustained resting SBP over 140 mmHg and a sustained DBP greater than 90 mmHg (CPG Secretariat MOH, 2014; Hall et al., 2012).

However, this definition has recently been updated by the American College of Cardiology/American Heart Association (ACC/AHA) in their 2017 guidelines. Table 2.2 shows the new 2017 American College of Cardiology and the American Heart Association (ACC/AHA) guidelines on categorization of BP in diagnosing hypertension. A person with SBP ≥ 130 mmHg and DBP ≥ 80 mmHg, or consumes antihypertensive medications to reach BP goals of SBP < 130 mmHg or DBP < 90 mmHg is termed as hypertensive (Muntner et al., 2018; Working Group on Hypertension CPG, 2018).

Table 2.2 Classification of BP according to the ACC/AHA guidelines (2017)

BP Category	SBP		DBP
Normal	<120 mmHg	and	<80 mmHg
Elevated	120-129 mmHg	and	<80 mmHg
Hypertension			
Stage 1	130-139 mmHg	or	80-89 mmHg
Stage 2	≥140 mmHg	or	≥90 mmHg

Many studies have found that a continuous relationship exists between elevated BP and disease risk (Whelton et al., 2017; Rahimi et al., 2015; Santulli, 2013). BP has steadily become the leading determinant of morbidity and mortality worldwide, being responsible for an even greater burden of disease than that conferred by smoking (Abdissa et al., 2015; Lim et al., 2012). There is also increasing evidence showing that the CVD risk associated with elevation of BP above approximately 115/75 mmHg increases in a log-linear fashion (Giles et al., 2009; Rahimi et al., 2015). Thus, a large component of the burden associated with non-optimal BP occurs among high-risk individuals who could not usually be classified hypertensive and, therefore, not considered for antihypertensive treatment (Abdissa et al., 2015; CPG Secretariat MOH, 2014).

Additionally, an increasing number of studies, both individual and meta-analyses of observational data have recorded a rising of progressively higher CVD risk going from normal BP to elevated BP and stage 1 hypertension, which was consistent across subgroups defined by gender and race or ethnicity (Whelton et al., 2017). These arguments and mounting new evidence from recent randomized controlled trials (RCTs) that focused on hypertension led to this new categorization of hypertension.

Risk Factors for Hypertension

Hypertension is a multifactorial disease with numerous risk factors that can be classified into modifiable and non-modifiable factors. A non-exhaustive list of these risk factors is shown in Table 2.3.

Table 2.3 Risk factors associated with hypertension

Modifiable risk factor	Non-modifiable risk factor
Obesity	Age
Alcohol	Gender
Lack of exercise	Genetic factors
Chronic stress	Ethnicity
Cigarette smoking	
High sodium intake	

(Bazzano, 2015; Bee Kiau et al., 2013; Go et al., 2013)

Hypertension can be classified as either primary or secondary, according to the etiologies causing it. Primary or essential hypertension is usually defined as elevated BP in which no obvious secondary cause for the increased BP is identified, accounting for the majority of adult cases (82-95%); whereas secondary hypertension accounts for only 2-10% of cases (Carey, 2008; Chen et al., 2012; Lankhorst et al., 2013).

Secondary hypertension is caused by multiple aetiologies; some have a definite genetic basis, others are caused by CVD and target organ injuries correlated with various disorders such as kidney disease and DM. In several cases, impaired BP can also develop as an effect from drugs or treatments received by the patients (Arima et al., 2011; Hall et al., 2012).

Many studies have contributed to the knowledge that genetic component plays a major role in the development of primary hypertension (Carey, 2008; Hall et al., 2012). However, identification of genes that importantly contribute to human primary hypertension still needs further research. Thus far, genetic studies of hypertension has been limited to identification of monogenic forms of hypertension which include familial hyperaldosteronism type I/glucocorticoid remediable aldosteronism (GRA), familial hyperaldosteronism type I/glucocorticoid

remediable aldosteronism (GRA), familial hyperaldosteronisms type II, Liddle syndrome, congenital adrenal hyperplasia (CAH), apparent mineralocorticoid excess (AME), pseudohypoaldosteronism type II, mineralocorticoid receptor activating mutation, and other conditions in which single-gene mutations fully explain the pathophysiology of hypertension (Hall et al., 2012).

Although it is currently known that over 25 rare mutation and 120 single-nucleotide polymorphisms of genetic variants contributes to BP and hypertension, each gene variants only has a small impact on BP. Collectively, the effect of all BP loci identified through genome-wide association studies accounts for only about 3.5% of BP variability (Whelton et al., 2017). However, it has been suggested that hypertension occurs as a result of additive effects of these multiple variant genes working en masse, and in concert in the presence of the necessary environmental

conditions to elevate BP (Hall et al., 2012), rendering essential hypertension as a complex polygenic disorder.

Excess alcohol consumption, poor physical fitness or sedentary lifestyle, insufficient intake of potassium, calcium, magnesium, protein (especially from vegetables), fiber, and fish fats, excess sodium intake, and overweight and obesity are among the key environmental factors that are responsible for the development of hypertension (Burnier & Wuerzner, 2015; Carey, 2008; Hall et al., 2012; Whelton et al., 2017). It is important to note that overweight and obesity are major contributors of the development of hypertension, accounting for as much as 65-78% of the risk (Hall et al., 2012)

Pathophysiology of hypertension

The pathophysiology of hypertension is complex and most likely involves complex interplay between renal, neural, cardiovascular, and endocrine factors modulated by genetic and environmental factors. For the purpose of this review the main mechanisms of hypertension have been divided into:

1. Endothelial dysfunction
2. Other mechanisms of hypertension

Endothelial dysfunction in essential hypertension

The endothelium is a thin layer of simple squamous epithelial tissue that lines the internal surface of the blood vessel interface between the bloodstream and the blood vessels. Healthy endothelial function is crucial in maintaining the normal cardiovascular homeostasis. The endothelium maintains blood vessel size by regulating smooth muscle tone, preventing the activation of clotting factors and platelet adhesion (Sherwood, 2010).

Moreover, the endothelium acts as a receptor-effector organ that responds to each physical or chemical stimulus and maintains vasomotor balance, as well as vascular-tissue homeostasis. It is sensitive to both mechanical and hormonal stimuli. The endothelium releases mediators that regulate vasomotor action, affects homeostasis and triggers inflammatory response, in the presence of stimuli. It is able to produce various types of molecules that work by counteracting each other to achieve a bidirectional balance of effects (Figure 2.6). An imbalance of these factors leads to hypertension via specific mechanisms which will be discussed in detail in a later section.

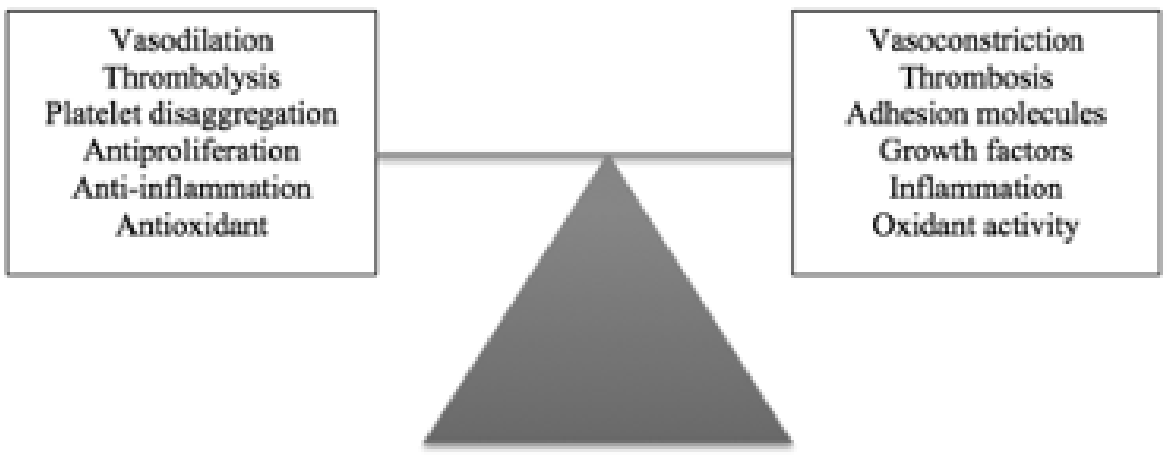

Figure 2.6 Regulatory functions of the endothelium

Sympathetic hyperactivity and its relationship with hypertension has previously been studied as one of the pathophysiological pathways of essential hypertension. Direct estimation of sympathetic activity is performed by microneurography and also measuring NA levels. These methods will assess the increased potentiation of central, cardiac and renal NA release in hypertensive patients, including those with aggravated hypertensive complications of target organ damage (Grassi et al., 2010; Parati & Esler, 2012).

The kidney is an organ that plays a crucial role in BP control as it regulates extracellular volume homeostasis through pressure-natriuresis mechanism. A defect in this mechanism, either caused by intrarenal or extrarenal disturbances causes a shift of the BP set point, resulting in hypertension. Intrarenal disturbances reduce glomerular filtration rate (GFR) or increase tubular reabsorption while extra-renal disturbances such as increased SNS activity, excessive formation of anti-natriuretic hormones or deficiency of natriuretic influences on the kidneys reduce the ability of the kidney to excrete sodium and water. The BP is increased in these situations to help maintain glomerulo-tubular balance and normal rates of salt and water excretion, so that it is equal to intake, despite abnormal kidney function (Burnier & Wuerzner, 2015; Hall et al., 2012).

SNS and RAAS are the most important neuroendocrine systems that are involved in increasing BP and maintaining the hypertension state, partially via their effects on renal function. Therefore, the crucial part the SNS plays in the pathogenesis of hypertension is through the activation of the renal sympathetic nerves (Bhatt et al., 2014). The redundant activation of the extensive nerves of the renal blood vessels, the juxtaglomerular apparatus, and the renal tubules causes sodium retention, increased renin secretion, and impaired renal pressure-natriuresis. However, the specific mechanisms that cause activation of the renal sympathetic nerves in primary hypertension are still unclear. Nevertheless, several mechanisms have been postulated to be responsible, including:

1. resetting of baroreceptor reflex
2. prolonged SNS activation by chronic stress
3. chronic SNS activation caused by obesity (Burnier & Wuerzner, 2015; Hall et al., 2012).

Meanwhile, the most important effect of RAAS on BP regulation is exerted by ANG II, which is a potent antinatriuretic. The mechanisms that mediate the potent antinatriuretic effects of ANG II include direct and indirect effects to increase tubular reabsorption as well as renal haemodynamic effects. Exceedingly high levels of ANG II will reduce renal excretory capability and impair pressure-natriuresis. Thus, BP needs to be increased in order to maintain sodium balance. Aldosterone is another powerful antinatriuretic hormone, which has important effects on pressure-natriuresis as those observed for ANG II. An excess in aldosterone secretion will render BP to become salt-sensitive so that there will be marked hypertension when sodium intake is normal or elevated, with minimal BP changes when sodium intake is low (Hall et al., 2012).

Hypertension has long since been associated with inflammation and the immune system. There are findings showing that increased levels of pro-inflammatory cytokines such as TNF-α and IL-6 correlate significantly with increased BP (Calabrò et al., 2009; LaMarca, 2012). Furthermore, recent studies showed that progression of hypertension is influenced by T cells activation promoted by neoantigens (molecules that are normally not exposed to the immune system and generate an immune response). Hypertensive stimuli, which initially cause a modest increase in BP, generate vascular and/or kidney injury; leading to neoantigens formation. T cells are then activated and penetrate both renal and vascular tissues. T-cell-derived signals such as IL-7 promote entry of other inflammatory cells such as macrophages, which release cytokines resulting in vasoconstriction and increased sodium and water reabsorption, therefore increasing the severity of hypertension (Tatasciore et al., 2008).

Eicosanoids have also been suggested to be the important regulators of sodium and water homeostasis as well as vascular function and hence, renal pressure-natriuresis and BP. Intrarenal prostaglandins (PGs) are also involved actively in renal perfusion regulation and GFR, as well as in the regulation of renin secretion (Burnier & Wuerzner, 2015). Among the PGs , PGE2 controls sodium excretion through several mechanism including direct effects on renal tubules (Hall et al., 2012). Renal PGs also protect pre-glomerular vessels from excessive ANG II-induced vasoconstriction, whereby saving the renal haemodynamics and excretory function from impairment. Conversely, other prostaglandins at the vascular level such as thromboxane A2 and PGF2α cause vasoconstriction (Mendizábal et al., 2013).

Overweight and obesity have also been linked to the pathogenesis of hypertension. Obesity is associated with extracellular fluid volume expansion, increased tissue blood flow in many tissues, and an increases in CO. Moreover, there will be a concomitant increase in renal tubular sodium reabsorption as well as impaired pressure natriuresis in increased BP related to obesity. The important mechanisms in which renal function is altered in obesity hypertension are increased SNS activity, RAAS activation, and physical compression of kidneys by accumulated fat within and around the kidney as well as by increased abdominal pressure (Hall et al., 2012; Kotsis et al., 2010). Hyperinsulinemia, ANG II, increased levels of free fatty acids, impaired baroreceptor reflexes, chemoreceptor mediated reflexes activation associated with sleep apneoa, and release of adipokines such as leptin, TNF-α, and IL-6 have been suggested to mediate SNS activation in obesity (Hall et al., 2012; Silva et al., 2014).

PREGNANCY & HYPERTENSIVE DISORDERS OF PREGNANCY

PHYSIOLOGICAL CARDIOVASCULAR CHANGES IN PREGNANCY

During pregnancy, women undergo profound anatomical and physiological changes to cope with the increased physical and metabolic demands of their pregnancies. Every system in the body including the cardiovascular (Rang et al., 2008), respiratory (Hegewald & Crapo, 2011), haematological (Pavord & Hunt, 2010), renal (Hussein & Lafayette, 2014), gastrointestinal (Costantine, 2014) and endocrine (Tan & Tan, 2013) systems undergo important physiological alterations and adaptations. These changes are necessary foetal development and to allow the mother and foetus to survive the demands of childbirth.

Blood volume increases during pregnancy. The increase starts at around 6 weeks of gestation and reaches a maximal volume of 4700 to 5200 mL by 32 weeks of gestation (Ouzounian & Elkayam, 2012). This leads to an increase in the amount of blood returning to the heart (the preload). The afterload is reduced due to maternal vasodilatation. As a result, the SV, which is defined as the quantity of blood pumped into the aorta during each cardiac cycle, increases by 20–30% during pregnancy. Maternal HR increases early in pregnancy, peaking and plateauing in the third trimester, during which rates are 15-20 beats per minute higher (San-Frutos et al., 2011). Therefore, CO, which is calculated as a product of SV and HR is increased approximately by 30%-50% (Tan & Tan, 2013) whereby, CO can be considered a measure of the functional capacity of the heart (Ouzounian & Elkayam, 2012).

The decrease in vascular resistance also preferentially directs some 20% of total CO to the utero-placental vascular bed by term, amounting to a >10-fold or greater increase over levels present in the non-pregnant state (Osol & Moore, 2014; Rang et al., 2008). During pregnancy, the blood flow to uterus and placenta constitutes up to 25% of the CO and is important for the development of the foetus. In addition, the blood flow to the skin, kidneys and breasts also increases (Tan & Tan, 2013).

Generalised systemic vasodilation occurs during pregnancy; so despite a 40-50% increase in CO, MAP drops by about 10 mmHg to reach its lowest value by the last trimester. BP usually falls immediately after delivery, then tends to rise, reaching a peak three to six days post partum in both normotensive women and those with hypertension during pregnancy. Transient hypertension may occur post partum even after uncomplicated pregnancies secondary to pain, drugs, excess fluid administration, salt and water accumulated during pregnancy moving into the

intravascular compartment, or restoration of non-pregnant vascular tone (Bramham et al., 2013).

HYPERTENSIVE DISORDERS OF PREGNANCY

Even though the general definition of hypertension has been updated, hypertension in pregnancy is still defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg. An increase of SBP of 30 mmHg and DBP of 15 mmHg above baseline BP is no longer recognised as hypertension if absolute values are below 140/90 mmHg (Working Group on Hypertension CPG, 2018). HDP include chronic hypertension (CH) during pregnancy, gestational hypertension (GH) or previously known as pregnancy induced hypertension (PIH), pre-eclampsia (PE) and CH with superimposed PE (Hutcheon et al., 2011; Yelmizaitun et al., 2010). An additional category of white coat hypertension is also recognised (Tranquilli et al., 2014).

Chronic hypertension during pregnancy

Pre-existing hypertension or commonly termed as chronic hypertension during pregnancy is defined as a SBP ≥140 mmHg or DBP ≥90 mmHg that is diagnosed before pregnancy or before 20 weeks period of gestation, and which persists beyond 12 weeks post partum. This definition is taken because a majority of women may not have had their blood pressures measured nearing pregnancy, therefore in practice the first trimester blood pressure is used to define normal or high BP in these women. De novo hypertension first diagnosed in late gestation, after 20 weeks gestation, that fails to resolve after 12 weeks postpartum, is also considered chronic hypertension. (Hutcheon et al., 2011; Tranquilli et al., 2014).

Gestational hypertension

Gestational hypertension is defined as hypertension that develops in pregnancy without any of the abnormalities found in PE after 20 weeks gestation and which returns to normal within 12 weeks postpartum. The latter part of the definition means that this diagnosis is made retrospectively in the postpartum period. GH mostly runs a benign course but up to 25% may develop PE (Hutcheon et al., 2011; Tranquilli et al., 2014; Working Group on Hypertension CPG, 2018).

Pre-eclampsia

Pre-eclampsia (PE) is a systemic syndrome that is typically characterised by new onset hypertension and proteinuria in pregnancy (with proteinuria defined as the urinary excretion of >300 mg of protein in 24 h) (Working Group on Hypertension CPG, 2018). PE is characterised by poor placental perfusion and a systemic disease process involving multiple organ systems (Rang et al., 2008).

Recent guidelines of the The Malaysian Society of Hypertension (MSH) in 2018 recommend that a diagnosis of PE be made when hypertension arises after 20 weeks gestation and is accompanied by any one of the following complications; significant proteinuria, renal insufficiency (serum creatinine ≥ 90 μmol/l or oliguria); liver disease (raised transaminases and/or severe right upper quadrant or epigastric pain), hyperreflexia with clonus or severe headaches, persistent visual disturbances (scotoma); haematological disturbances such as thrombocytopenia, coagulopathy, haemolysis; or foetal growth restriction (Hypertension Guideline Working Group, 2018).

Chronic hypertension with superimposed pre-eclampsia

Chronic hypertension with superimposed pre-eclampsia is diagnosed when a woman with CH develops new onset proteinuria, thrombocytopaenia or any of the other systemic features of the PE syndrome. It is also diagnosed when there is sudden increase in the severity of hypertension, appearance of features of PE/eclampsia, and worsening proteinuria in a woman with pre-existing proteinuria early in gestation (Hutcheon et al., 2011; Working Group on Hypertension CPG, 2018).

White coat hypertension

White coat hypertension or isolated office hypertension is defined as elevated BP of ≥140/90 mmHg only in the clinic with normal BP demonstrated by ambulatory BP monitoring (ABPM) or home blood pressure monitoring (HBPM) either awake or during sleep. Studies in non-pregnant population showed that they are

comparable. Women with white coat hypertension should be considered high risk as they may progress to GH (50%) or PE (8%) (Tranquilli et al., 2014; Working Group on Hypertension CPG, 2018).

Postpartum hypertension

Few studies have reported the incidence of postpartum hypertension too. The incidence of new onset postpartum hypertension is unknown but it is estimated to occur in 0.3-28% of women (Bramham et al., 2013).

REFERENCES

Abdissa, S. G., Feleke, Y., & Awol, M. (2015). Prevalence of hypertension and pre-hypertension in Addis Ababa, Ethiopia: A survey done in recognition of World Hypertension Day, 2014. Ethiopian Journal of Health Development, 29, 22–30. doi:10.1161/CIRCULATIONAHA.115.018912

Arima, H., Barzi, F., & Chalmers, J. (2011). Mortality patterns in hypertension. Journal of Hypertension, 29, S3–S7. doi:10.1097/01.hjh.0000410246.59221.b1

Barret, K., Boitano, S., Barman, S., & Brooks, H. (2012). Ganong's review of medical physiology (24th ed.) Singapore: McGraw Hill Medical.

Bramham, K., Nelson-Piercy, C., Brown, M. J., & Chappell, L. C. (2013). Postpartum management of hypertension. BMJ, 346(February), f894–f894. doi:10.1136/bmj.f894

Burnier, M., & Wuerzner, G. (2015). Pathophysiology of Hypertension. Pathophysiology and Pharmacology of Cardiovascular Disease.

Calabrò, P., Limongelli, G., Riegler, L., Maddaloni, V., Palmieri, R., Golia, E., Calabrò, R. (2009). Novel insights into the role of cardiotrophin-1 in cardiovascular diseases. Journal of Molecular and Cellular Cardiology, 46(2), 142–148. doi:10.1016/j.yjmcc.2008.11.002

Carey, R. M. (2008). Pathophysiology of Primary Hypertension. Microcirculation, 794–895. doi:10.1016/B978-0-12-374530-9.00020-6

Chen, S. (2012). Essential hypertension. Journal of Hypertension, 30, 42–45. doi:10.1097/HJH.0b013e32834ee23c

Costantine, M. M. (2014). Physiologic and pharmacokinetic changes in pregnancy. Frontiers in Pharmacology, 5 APR(April), 1–5. doi:10.3389/fphar.2014.00065

CPG Secretariat MOH. (2014). CLINICAL PRACTICE GUIDELINES Management of Hypertension (Vol. 13, pp. 36–42).

Garovic, V. D., Bailey, K. R., Boerwinkle, E., Hunt, S. C., Weder, A. B., Curb, D., Turner, S. T. (2010). Disease Later in Life, 28(4), 826–833. doi:10.1097/HJH.0b013e328335c29a.Hypertension

Giles, T. D., Materson, B. J., Cohn, J. N., & Kostis, J. B. (2009). Definition and classification of hypertension: An update. Journal of Clinical Hypertension, 11(11), 611–614. doi:10.1111/j.1751-7176.2009.00179.x

Grassi, G., Seravalle, G., & Quarti-Trevano, F. (2010). The “neuroadrenergic hypothesis” in hypertension: Current evidence. Experimental Physiology, 95, 581–586. doi:10.1113/expphysiol.2009.047381

Hall, J. E., Granger, J. P., do Carmo, J. M., da Silva, A. a., Dubinion, J., George, E., Hall, M. E. (2012). Hypertension: Physiology and pathophysiology. Comprehensive Physiology, 2(October), 2393–2442. doi:10.1002/cphy.c110058

Hall, J. & Guyton, A. (2011). Guyton and Hall textbook of medical physiology (12th ed., pp.191-240). Philadelphia, PA: Saunders Elsevier. S.

Hegewald, M. J., & Crapo, R. O. (2011). Respiratory Physiology in Pregnancy. Clinics in Chest Medicine, 32(1), 1–13. doi:10.1016/j.ccm.2010.11.001

Hübner, C. a., Schroeder, B. C., & Ehmke, H. (2015). Regulation of vascular tone and arterial blood pressure: role of chloride transport in vascular smooth muscle. Pflugers Archiv European Journal of Physiology, 467, 605–614. doi:10.1007/s00424-014-1684-y

Hussein, W., & Lafayette, R. a. (2014). Renal function in normal and disordered pregnancy. Current Opinion in Nephrology and Hypertension, 23(1), 46–53. doi:10.1097/01.mnh.0000436545.94132.52

Hutcheon, J. a., Lisonkova, S., & Joseph, K. S. (2011). Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Practice and Research: Clinical Obstetrics and Gynaecology, 25(4), 391–403. doi:10.1016/j.bpobgyn.2011.01.006

Jacob, J., Chopra, S., & Baby, C. (2011). Neuro-endocrine regulation of blood pressure. Indian Journal of Endocrinology and Metabolism, 15, 281. doi:10.4103/2230-8210.86860

Klabunde, R. (2011). Cardiovascular Physiology Concepts (2nd ed.). Philadelphia, PA: Lippincott Williams & Wilkins/Wolters Kluwer.

LaMarca, B. (2012). Endothelial dysfunction. An important mediator in the pathophysiology of hypertension during pre-eclampsia. Minerva Ginecologica, 64(4), 309–320. doi:R09123394 [pii]

Lankhorst, S., Kappers, M. H. W., Van Esch, J. H. M., Danser, a. H. J., & Van Den Meiracker, A. H. (2013). Mechanism of hypertension and proteinuria during angiogenesis inhibition: Evolving role of endothelin-1. Journal of Hypertension, 31(3), 444–454. doi:10.1097/HJH.0b013e32835c1d1b

Muntner, P., Carey, R. M., Gidding, S., Jones, D. W., Taler, S. J., Wright, J. T., & Whelton, P. K. (2018). Potential U.S. Population Impact of the 2017 ACC/AHA High Blood Pressure Guideline. Journal of the American College of Cardiology, 71, 109–118. doi:10.1016/j.jacc.2017.10.073

Osol, G., & Moore, L. G. (2014). Maternal Uterine Vascular Remodeling During Pregnancy. Microcirculation, 21, 38–47. doi:10.1111/micc.12080

Ouzounian, J. G., & Elkayam, U. (2012). Physiologic Changes During Normal Pregnancy and Delivery. Cardiology Clinics, 30(3), 317–329. doi:10.1016/j.ccl.2012.05.004

Parati, G., & Esler, M. (2012). The human sympathetic nervous system: Its relevance in hypertension and heart failure. European Heart Journal, 33, 1058–1066. doi:10.1093/eurheartj/ehs041

Patton, K. T., & Thibodeau, G. A. (2010). Anatomy and Physiology. Mosby/Elsevier. Retrieved from https://books.google.com.my/books?id=6vJLAQAAIAAJ

Pavord, S., & Hunt, B. (2010). The Obstetric Hematology Manual.

Pimenta, E., & Calhoun, D. a. (2010). Treatment of resistant hypertension. Journal of Hypertension, 28, 2194–2195. doi:10.1097/HJH.0b013e32833eafa3

Rahimi, K., Emdin, C. a., & MacMahon, S. (2015). The Epidemiology of Blood Pressure and Its Worldwide Management. Circulation Research, 116, 925–935. doi:10.1161/CIRCRESAHA.116.304723

Rang, S., van Montfrans, G. a., & Wolf, H. (2008). Serial hemodynamic measurement in normal pregnancy, preeclampsia, and intrauterine growth restriction. American Journal of Obstetrics and Gynecology, 198(May), 1–9. doi:10.1016/j.ajog.2007.11.014

Rautureau, Y., & Schiffrin, E. L. (2013). Endothelin system: roles in hypertension. Hypertension, 102–115. doi:10.2217/EBO.12.169

San-Frutos, L., Engels, V., Zapardiel, I., Perez-Medina, T., Almagro-Martinez, J., Fernandez, R., & Bajo-Arenas, J. M. (2011). Hemodynamic changes during pregnancy and postpartum: A prospective study using thoracic electrical bioimpedance. Journal of Maternal-Fetal and Neonatal Medicine, 24(November), 1333–1340. doi:10.3109/14767058.2011.556203

Santulli, G. (2013). Epidemiology of cardiovascular disease in the 21st century: updated numbers and updated facts. Online JCvD, 11(1), 2326–3121. doi:10.1016/j.proci.2004.08.222

Sherwood, L. (2010). Human physiology, (7th ed., pp. 345-353, 369-373). Australia: Thomson/Brooks/Cole.

Silva, A. a, Carmo, J. M., & Hall, J. E. (2014). Role of Leptin and CNS Melanocortins in Obesity Hypertension, 22(2), 135–140. doi:10.1097/MNH.0b013e32835d0c05.Role

Tan, E. K., & Tan, E. L. (2013). Alterations in physiology and anatomy during pregnancy. Best Practice and Research: Clinical Obstetrics and Gynaecology, 27(6), 791–802. doi:10.1016/j.bpobgyn.2013.08.001

Tatasciore, A., Zimarino, M., Renda, G., Zurro, M., Soccio, M., Prontera, C., De Caterina, R. (2008). Awake Blood Pressure Variability, Inflammatory Markers and Target Organ Damage in Newly Diagnosed Hypertension. Hypertension Research, 31(December), 2137–2146. doi:10.1291/hypres.31.2137

Tranquilli, a. L., Dekker, G., Magee, L., Roberts, J., Sibai, B. M., Steyn, W., Brown, M. a. (2014). The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP. Pregnancy Hypertension, 4, 97–104. doi:10.1016/j.preghy.2014.02.001

Wang, W., Li, C., Summer, S., Falk, S., & Schrier, R. W. (2010). Interaction between vasopressin and angiotensin II in vivo and in vitro: effect on aquaporins and urine concentration. AJP: Renal Physiology, 299, F577–F584. doi:10.1152/ajprenal.00168.2010

Wehrwein, E. a., & Joyner, M. J. (2013). Regulation of blood pressure by the arterial baroreflex and autonomic nervous system. Handbook of Clinical Neurology (1st ed., Vol. 117, pp. 89–102). Elsevier B.V. doi:10.1016/B978-0-444-53491-0.00008-0

Whelton, P. K., Carey, R. M., Aronow, W. S., Casey, D. E., Collins, K. J., & Himmel, C. D. (2017). 2017 Guideline for the Prevention, Detection, Evaluation, and Management 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Journal of the American College of Cardiology, 70, 1785–1822. doi:10.1016/j.jacc.2017.07.745

World Health Organization. (2017). World health statistics 2017: Monitoring Health for the SDGs. Geneve: World Health Organization.

Yelmizaitun O., Jeriah I., Huraini H., N. Mazlina M., T. Zailina T.N., Norashidah A., M. Salwani., Norlaila., K. N. (2010). Fetal - Maternal Outcome among pregnancy induced hypertension mothers attending Klinik Kesihatan Rantau Panjang in 2010. JKN Kelantan. Retrieved from http://jknkelantan.moh.gov.my/v3/uploads/files/pdfs/khc2011/OP_24.pdf

Yokoyama, T., Nakamuta, N., Kusakabe, T., & Yamamoto, Y. (2015). Sympathetic regulation of vascular tone via noradrenaline and serotonin in the rat carotid body as revealed by intracellular calcium imaging. Brain Research, 1596, 126–135. doi:10.1016/j.brainres.2014.11.037