CHAPTER II

REVIEW OF LITERATURE
1. ELDERLY AND AGING

Globally, 10% (600 million) of the world’s population is elderly and it is expected to increase to 21% (1.97 billion) in 2051 (Department of economic and social affairs, New York, United Nations. World Population Ageing; 1950-2050). Demographically, Asia is the most important continent in the world, where the population is growing both larger and older. The population of elderly aged above 65 years in Asia is expected to increase by four fold to about 1 billion by 2050 (National Research Council., 2012). About 34% of the world’s older population is present in India and China; the two most populous countries in the world. India is the second largest country in the world with about 76 million elderly persons above 60 years of age compared to China’s 127 million (National Research Council., 2012; Census of India., 2001). India’s older population is estimated to grow from close to 8% (76 million) to about 9% (113 million) in 2016, and almost 20% in 2050 (Kowal P et al., 2012).

There are medical conditions due to age-related physiological changes that occur exclusively among the elderly which affect the quality of life. The diseases associated with older age groups are often non-communicable diseases (NCDs) that include CV diseases (hypertension, heart attacks and stroke), cancers, chronic respiratory diseases (such as chronic obstructed pulmonary disease and asthma) and diabetes (Boutayeb A & Boutayeb S., 2005; Hunter DJ & Reddy KS., 2013). The NCDs were once more prevalent in industrialized countries, but is now greater in the low and middle-income countries than high income countries. The rapid economic growth accompanied by rapid urbanization with unhealthy diet and life-style may contribute to the increase of non-communicable diseases in rapidly developing countries like India and China (Kowal P et al., 2012). NCDs are the leading cause of death in older individuals. Among the NCDs, CV diseases account for the largest fraction of deaths followed by cancer, chronic respiratory diseases and diabetes (Hunter DJ & Reddy KS., 2013). Hypertension is one of the major risk factor and treatable cause for CV morbidity and mortality in older individuals (Fagard RH., 2002; National High Blood Pressure Education Program Working Group., 1994; Hypertension Study Group., 2001). Hypertension in most of the elderly individuals is accompanied by multiple comorbidities, which tremendously affect their management. The recent emphasis on studies pertaining to the elderly in the developing world is attributed to the increasing number of older individuals and
their associated deteriorating conditions. Hence, the scientific understanding to improve the quality of life in elderly is the need of the hour.
2. HYPERTENSION IN ELDERLY

2.1. Introduction

Increased age is an established CV risk factor. High blood pressure is the most common cause of CV morbidity and mortality. Aging and high BP leads to structural and functional changes in the heart and vascular system. Hence, aging along with hypertension is a major & strong risk factor for CV morbidity and mortality (Lewington S et al., 2002; Fagard RH., 2002). It has the greatest impact on globally attributable mortality of any other risk factor and accounts for the 3rd leading cause of global burden of disease (Supiano MA., 2009). A change in the patterns of hypertension with age has been observed. In elderly, SBP increases without much change in DBP, which is categorized as isolated systolic hypertension (ISH) leading to widening of PP. Systolic hypertension may lead to stroke, myocardial infarction, dementia, renal failure and death (Zeiman SJ et al., 2005). These clinical complications affect the quality and longevity of life in elderly. According to World Health Organization, the most common cause of preventable death in developed countries is hypertension, which is significantly increasing in developing countries (Ezzati M et al., 2002). Reduction of SBP by 10 mmHg and DBP by 5 mmHg at age 65 years is associated with a decrease in myocardial infarction by 25%, stroke by 40%, congestive heart failure (CHF) by 50%, and overall mortality by 10-20% (Law M et al., 2003; Supiano MA., 2009).

2.2. Epidemiology

The prevalence of hypertension in elderly ranges from 50% to 75% and it is estimated that two out of three individuals over 75 years of age suffer from hypertension (Supiano MA., 2009; Lloyd-Sherlock P et al., 2014). According to the Framingham Heart Study, about 60% of the population by age 60 develops hypertension. In the same study, it was also estimated that the prevalence of hypertension may increase to about 65 % in men and 75 % in women by age 70. Also, it has been observed that nearly 85% of individuals with normal BP upto the age of 55 were later developed hypertension over 20-25 years (their residual lifetime risk) of follow-up study (Levy D et al., 1996; Vokonas PS et al., 1988). According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7), two thirds of individuals after 65 years have hypertension.
(Chobanian AV, JNC 7., 2003). From an Indian perspective, the prevalence of hypertension in elderly above 60 years was reported between 40% and 60% (Radhakrishnan S et al., 2013; Kalavathy MC et al., 2000; Chinnakali P et al., 2013). There was wide difference in the prevalence rates reported from various regions of India. The prevalence rates were shown higher in elderly women compared to men (Supiano MA., 2009; Chinnakali P et al., 2013).

2.3. Classification of hypertension

There are two classifications of hypertension proposed by two societies in their guidelines for management of hypertension: (1) European Society of Hypertension and European Society of Cardiology (ESH/ESC-2007 and 2009 update) and (2) Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.

<table>
<thead>
<tr>
<th>Classification</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
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<tbody>
<tr>
<td>Optimal</td>
<td>≤ 120</td>
<td>And ≤ 80</td>
</tr>
<tr>
<td>Normal</td>
<td>120-129</td>
<td>80-84</td>
</tr>
<tr>
<td>High normal</td>
<td>130-139</td>
<td>85-89</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Grade 1 (mild)</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>2. Grade 2 (moderate)</td>
<td>160-179</td>
<td>100-109</td>
</tr>
<tr>
<td>3. Grade 3 (severe)</td>
<td>≥ 180</td>
<td>≥ 100</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>≥ 140</td>
<td>≤ 90</td>
</tr>
</tbody>
</table>

SBP: Systolic blood pressure; DBP: Diastolic blood pressure

As per the guidelines of ESH and ESC (2007 and 2009 update), hypertension has been classified into Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) and isolated systolic hypertension (Table 1). Isolated systolic hypertension should be graded (grades 1, 2 and 3) on the basis of SBP values in the ranges indicated in the Table 1.

Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure in its 7th report (JNC-7) defined criteria for normal BP and classified hypertension into prehypertension, Stage 1 hypertension and Stage 2 hypertension (Table 2). As JNC-7
omitted the isolated systolic hypertension and since isolated diastolic hypertension is so uncommon among older individuals, one may correctly classify an older patient’s hypertension based entirely on the level of their SBP into: Stage 1 hypertension between 140 and 159 mmHg systolic and Stage 2 hypertension, ≥ 160 mmHg systolic.

Table 2 Classification of blood pressure for adults according to JNC7 guidelines

<table>
<thead>
<tr>
<th>Classification</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≤ 120</td>
<td>And ≤ 80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>Or 80-89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140-159</td>
<td>Or 90-99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>≥ 160</td>
<td>Or ≥ 100</td>
</tr>
</tbody>
</table>

SBP: Systolic blood pressure; DBP: Diastolic blood pressure

2.4. Types and Definitions of hypertension

2.4.1. Essential hypertension

Essential, primary or idiopathic hypertension can be defined as a rise in BP of unknown cause that increases risk for cerebral, cardiac, and renal events (Messerli FH et al., 2007). It accounts for 95% of all cases of hypertension. Essential hypertension is a heterogeneous disorder, with different patients having different causal factors that lead to high BP (Carretero OA & Oparil S et al., 2000).

2.4.2. Secondary hypertension

Secondary hypertension is a type of hypertension with an underlying, potentially curable cause (Table 3). The prevalence of secondary hypertension varies by age group. The prevalence of secondary hypertension ranges between 5 & 10% (Chiong JR et al., 2008). The etiology for secondary hypertension also varies by age group. The most common secondary cause for hypertension in young adults (particularly women) is renal artery stenosis, in
middle-aged adults is aldosteronism and in older adults is atherosclerotic renal artery stenosis (Viera AJ et al., 2010).

**Table 3 Causes of secondary hypertension**

<table>
<thead>
<tr>
<th>Causes</th>
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</thead>
<tbody>
<tr>
<td>1. Coarctation of aorta</td>
</tr>
<tr>
<td>2. Renal artery stenosis</td>
</tr>
<tr>
<td>3. Thyroid disorders</td>
</tr>
<tr>
<td>4. Aldosteronism</td>
</tr>
<tr>
<td>5. Obstructive sleep apnea</td>
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<tr>
<td>6. Pheochromocytoma</td>
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<tr>
<td>7. Cushing syndrome</td>
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<tr>
<td>8. Drugs (NSAID, alcohol, estrogen)</td>
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</tbody>
</table>

**2.4.3. White-coat hypertension**

It is defined as the presence of an elevated BP (≥140/90 mmHg) in an office/clinic setting or in medical environment, but with normal BP when measured at home or normal day time ambulatory BP (≤135 mmHg systolic & ≤85 mmHg diastolic). It is also called as ‘isolated office or clinic hypertension’. It is more common in the elderly (Celis H & Fagard RH., 2004; Verdecchia P et al., 2002).

**2.4.4. Isolated ambulatory or Masked hypertension**

It is defined as the presence of a normal BP in an office/clinic setting or in medical environment, but with elevated BP when measured at home or day time ambulatory BP (≥135 mmHg systolic & ≥85 mmHg diastolic) (Pickering TG et al., 2007). It is associated with an increased risk of CV events. It is frequent in the elderly and is associated with a high vascular profile, so measurement of BP at home is suggested in this age segment (Caddiolati C et al., 2011).
2.4.5. Pseudohypertension

It is a condition in which indirect BP measured by the cuff method (Osler’s Sign) overestimates the true intra-arterial BP (Kuwajima I et al., 1990). Systolic BP is falsely increased by atherosclerotic and other vascular changes associated with age (Foran TG et al., 2004). As, the measurement of BP depends on measuring on how much force it takes to compress an artery, so to compress the stiffened arteries the sphygmomanometer reading is falsely increased. Pseudohypertension is suspected when we found very high BP without any signs of organ damage or other complications, or occurrence of features of hypotension (dizziness, confusion or decreased urine output) when treated with antihypertensive. It occurs frequently in the elderly irrespective of them being hypertensive. The Osler Manaeuver, a sphygmomanometric procedure can be performed if pseudohypertension is suspected in the elderly, but it has low sensitivity and specificity. If the radial artery pulse remains palpable even after inflating the cuff above systolic pressure indicates false hypertension (Wright JC & Looney SW et al., 1997). Psuedohypertension can be confirmed by direct intra-arterial measurement of BP (Spence JD., 1997; Foran TG et al., 2004).

2.4.6. Resistant hypertension

It is defined as BP that remains uncontrolled despite of the concurrent use of 3 optimally dosed antihypertensive agents of different classes (Vongpatanasin W., 2014). One of the three antihypertensive agents should be diuretic. It is prevalent among all ages, but is more prevalent in elderly hypertensive patients (Calhoun DA et al., American Heart Association Statement., 2008). Patients who are well controlled but require four or more medications were also considered as resistant hypertension as per American heart association (AHA) statement and JNC-7 guidelines. There are several factors and causes which contribute to resistant hypertension (Table 4).

2.4.7. Dipper or non-dipper patient

Normally, the BP falls at night compared to daytime. The individuals who fail to decrease their nocturnal BP by at least 10% relative to their daytime BP are referred to as non-dippers. They have been shown to have greater CV disease risk compared to those with the normal dipper pattern (decrease in blood pressure at night compared to daytime). This diurnal
variation correlates with variations in sympathetic nervous activity associated with other factors such as age, hypertensive status, quality of sleep, marital status and socioeconomic status (Holt-Lunstad J et al., 2009). The prevalence of non-dippers is higher in the elderly population (Aronow WS et al., 2011).

**Table 4** Factors those contribute to resistant hypertension

<table>
<thead>
<tr>
<th>1 Patient characteristics associated with resistant hypertension</th>
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<tbody>
<tr>
<td>Older age</td>
</tr>
<tr>
<td>High baseline blood pressure</td>
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<tr>
<td>Obesity</td>
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<tr>
<td>Excessive dietary salt ingestion</td>
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<tr>
<td>Chronic kidney disease</td>
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<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
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<tr>
<td>Black race</td>
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<tr>
<td>Female sex</td>
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<table>
<thead>
<tr>
<th>2 Factors contributing resistant hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor patient adherence</td>
</tr>
<tr>
<td>Physical inertia</td>
</tr>
<tr>
<td>Lack of adherence to life-style modifications</td>
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<tr>
<td>Inadequate doses</td>
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<tr>
<td>Inappropriate combinations of antihypertensive drugs</td>
</tr>
<tr>
<td>Excess alcohol intake</td>
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</tbody>
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<table>
<thead>
<tr>
<th>3 Secondary causes of resistant hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Renal parenchymal disease</td>
</tr>
<tr>
<td>Primary aldosteronism</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Cushing’s disease</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
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<tr>
<td>Aortic coarctation</td>
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<tr>
<td>Intracranial tumor</td>
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2.5. Pathophysiology of hypertension

Homeostatic regulation of BP within its normal range to ensure an adequate tissue blood flow requires co-ordination of several complex interacting physiological systems. Perturbation in this complex regulatory system results in change in the normal baseline of BP. There are diverse mechanisms (Figure 1) and age-associate physiological changes that likely contribute to the development of essential hypertension in elderly (Table 5 & Figure 2). Lifestyle factors such as high sodium containing diet, being sedentary and obesity also contributes to an elevation in BP in older individuals. The hallmark of hypertension in the elderly is increased vascular resistance.

Figure 1 Pathophysiology of hypertension
Table 5 Age-associated factors contributing to hypertension

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Arterial stiffness or decreased vascular compliance</td>
</tr>
<tr>
<td>2</td>
<td>Endothelial dysfunction</td>
</tr>
<tr>
<td>3</td>
<td>Increased sympathetic nervous system activity</td>
</tr>
<tr>
<td>4</td>
<td>Decreased baroreceptor sensitivity</td>
</tr>
<tr>
<td>5</td>
<td>Decreased alpha- and beta-adrenergic receptor responsiveness</td>
</tr>
<tr>
<td>6</td>
<td>Decreased ability to excrete sodium load (sodium sensitivity)</td>
</tr>
<tr>
<td>7</td>
<td>Low plasma renin activity</td>
</tr>
<tr>
<td>8</td>
<td>Resistance to insulin’s effect on carbohydrate metabolism</td>
</tr>
<tr>
<td>9</td>
<td>Increase in aldosterone</td>
</tr>
<tr>
<td>10</td>
<td>Increase in oxidative stress</td>
</tr>
<tr>
<td>11</td>
<td>Central adiposity</td>
</tr>
</tbody>
</table>

(Reference: Supiano MA., 2009)

2.5.1. Age-associated structural change in arterial system: Arterial stiffness

The idea of Sir William Osler (1898) that has been stated 100 years before still holds true on association of vascular health and longevity. Sir William Osler states that “Longevity is a vascular question, which has been well expressed in the axiom that man is only as old as his arteries. To a majority of men death comes primarily or secondarily through this portal. The onset of what may be called physiological arteriosclerosis depends, in the first place, upon the quality of arterial tissue which the individual has inherited, and secondly upon the amount of wear and tear to which he has subjected it.”

Blood vessel walls, especially large elastic arteries stiffen with age. In younger individuals, aorta and the proximal elastic arteries dilate by approximately 10% in response to each beat, while the muscular arteries dilate by only about 3% with each beat (O’Rourke MF & Hashimoto J., 2007). The heterogeneity in stiffness process with age between proximal and distal arteries can be explained on the basis of severity of fatigue exerted by the different degree of stretch (O’Rourke MF & Hashimoto J., 2007; Lionakis N et al., 2000).
The reduction of vascular compliance with age due to stiffening of arteries is the major contributor for elevation of BP, especially systolic pressure resulting in isolated systolic hypertension in elderly. Aging has been associated with both structural and
functional changes in the arterial system. Two major age-related structural changes that take place in elastic arteries are stiffness and dilatation. These changes result in decline or failure in expansion of aorta in response to ventricular systole which leads to elevation in systolic pressure and failure to recoil results in reduction in DBP thus causing widening of PP (Lee HY & Oh BH., 2010). Hence, an increase in PP, a pulsatile component creates a greater pulsatile stress on the arterial system even in the normotensive individuals (Millar JA et al., 2000).

The causes of arterial stiffness are summarized in the figure 3. The principal structural change with age occurs in the intima (hyperplasia) and the media (degeneration). The structural changes in the media of elastic arteries (medial degeneration) include increase in collagen content and cross linking, increase in elastin fragmentation and decrease in elastin content (Lim MA & Townsend RR et al. 2009). The age-related structural changes in the elastin (thinning and fragmentation) and collagen are not seen in the muscular arteries. These changes in media are associated with increased expression of matrix metalloproteinases (MMPs). Matrix metalloproteinases regulate collagen and elastin molecules of the vessel wall. The factors those determine the stiffness of arteries and its ability to expand and recoil are structural proteins and pressure exerted by blood on their wall (Cecelja M &

![Figure 3 Causes of arterial stiffness (Reference: Lee HY & Oh BH., 2010)](image-url)

Arterial stiffness also occurs from deposition of advanced glycation end products (AGE) on the proteins leading to alteration in their physical properties. Calcium deposition in the arterial wall might also contribute to reduction in the vascular compliance with age, particularly after the 5th decade (Atkinson J., 2008).

The functional change in the arterial system that contributes to stiffness is age-associated deterioration in endothelial function (Jin RC & Loscalzo J., 2010). Impaired vasomotor function associated with endothelial dysfunction leads to thickening of the intima-media layer, especially in the peripheral muscular arteries and can contribute to increase in peripheral vascular resistance, a pathognomonic characteristic of hypertension in the elderly population (Taddei S et al., 2001; Torregrossa AC et al., 2011). It has been reported that aside from extracellular matrix, increased vascular stiffness with aging is also attributable to intrinsic changes in vascular smooth muscle cells (VSMCs) by increasing the expression of adhesion molecule (Qiu H et al., 2010).

Arterial stiffness is an independent and strong predictor of CV morbidity and mortality in hypertensives without any overt CV disease (Blacher J et al., 1999; Laurent S et al., 2001) and also in well-functioning older adults (Sutton-Tyrrell K et al., 2005).

A number of genetic factors which influences arterial stiffness have also been identified. Polymorphic variation in the fibrillin-1 (Medley TL et al., 2002), angiotensin II type-1 receptor (Lajemi M et al., 2001) and endothelin receptor genes were found associated with vascular stiffness (Lajemi M et al., 2001).

2.5.2. **Age-associated functional changes in arterial system: vascular endothelial dysfunction**

Age also affects the regulation of vascular resistance by vascular endothelium. Vascular endothelium is a thin single layer of endothelial cells that lines the innermost surface of the entire vascular system i.e. all the blood vessels. In adults, approximately ten trillion (10^{13})
cells form an ‘organ’ with a large surface of approximately about $350m^2$ area and about 110 g weight (Pries AR & Kuebler WM., 2006). Endothelial cell structure and functional integrity are important for various vital CV functions and integrity (Galley HF & Webster NR., 2004). The vasodilator function of endothelium was first demonstrated by Furchgott and Zawadki in 1980. They demonstrated that the removal of endothelial layer of isolated arteries prevents the in vitro dilator response to acetylcholine (Furchgott RF & Zawadzki JV., 1980). The key factor responsible for arterial relaxation was first discovered as endothelium derived relaxing factor (EDRF) and later identified it as NO (Vanhoutte PM et al., 2009). Nitric oxide, a key determinant of vascular homoeostasis, is a simple molecule that regulates vascular tone, vascular permeability and antithrombotic properties (Jin RC & Loscalzo J., 2010).

A. Functions of vascular endothelium

The endothelium is a highly dynamic cell layer that is involved in a multitude of physiological functions, including regulation of perfusion, fluid and solute exchange, haemostasis and coagulation, inflammatory responses, vasculogenesis and angiogenesis (Aird WC., 2004; Pries AR & Kuebler WM., 2006). Endothelium by secreting various mediators is involved in both synthetic and metabolic functions (Table 6).

1. **Vascular homoeostasis**: Vascular endothelium regulates several physiological properties of the blood vessel, including vasodilation, vascular permeability and antithrombotic properties. Nitric oxide is key determinant of vascular health (Jin RC & Loscalzo J., 2010).

2. **Haemostasis and coagulation**: Vascular endothelium is critical for protecting against vascular injury and maintaining blood fluidity. Normal endothelium produces a number of substances which regulate haemostasis and coagulation: (a) Prostacyclin and nitric oxide are vasodilators and potent inhibitors of platelet and monocyte activation. Normal endothelial surface inhibits platelet aggregation. (b) Thrombomodulin serves as a binding site for thrombin to activate protein C and heparin-like molecules serve as a cofactor for antithrombin III. (c) Tissue plasminogen activator activates the fibrinolysis system. (d) von Willebrand factor mediates platelet adhesion and shear-stress-induced
Table 6 Products of vascular endothelial cells

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Vasodilator Factors</td>
<td>Nitric oxide, Prostacyclin (PGI₂), Endothelium derived hyperpolarization</td>
</tr>
<tr>
<td></td>
<td>factor (EDHF)</td>
</tr>
<tr>
<td>2. Vasoconstricting factors</td>
<td>Endothelin (ET), Thromboxane A₂ (TXA₂), Angiotensin converting enzyme</td>
</tr>
<tr>
<td></td>
<td>Leukotrienes, Free radicals or Reactive oxygen species (ROS)</td>
</tr>
<tr>
<td>3. Procoagulant factors</td>
<td>Von Willebrand factor, Thromboxane A₂, Thromboplastin, Factor V, Platelet activating factor, Plasminogen activator inhibitor</td>
</tr>
<tr>
<td>4. Antithrombotic factors</td>
<td>Prostacyclin, Thrombomodulin, Antithrombin, Plasminogen activator, Heparin</td>
</tr>
<tr>
<td>5. Growth factors</td>
<td>Insulin like growth factor, Transforming growth factor, Colony stimulating factor</td>
</tr>
<tr>
<td>6. Lipid metabolism</td>
<td>LDL-receptor, Lipoprotein lipase</td>
</tr>
<tr>
<td>7. Matrix products</td>
<td>Fibronectin, Laminin, Collagen, Proteoglycans, Proteases</td>
</tr>
<tr>
<td>8. Inflammatory mediators</td>
<td>Interleukins 1,6,8, Leukotrienes, Major histocompatibility complex class II (MHC II)</td>
</tr>
</tbody>
</table>

(Reference: Modified, Galley HF & Webster NR., 2004)
aggregation. Endothelial injury results in loss of protective substances and expression of adhesive molecules, procoagulant activities, and mitogenic factors leading to thrombosis formation and atherosclerosis (Wu KK & Thiagarajan P., 1996).

3. **Vascular tone & blood pressure**: Endothelial cells by secreting a number of vasodilators (NO, prostacyclin) and vasoconstrictors (endothelin, thromboxane A2) regulates vascular tone and BP.

4. **Angiogenesis**: Angiogenesis refers to the growth of new blood vessels (or damaged blood vessels) from pre-existing endothelium. Vascular endothelium produces vascular endothelial growth factor (VEGF) which mediates angiogenesis.

5. **Barrier function**: Tight junction between endothelial cells acts as a ‘gate’ or semi-selective barrier between the blood and surrounding tissue, and controls the passage of substances, leucocytes, ions and water into and out of the blood stream. Increased vascular permeability leads to oedema.

6. **Anti-inflammation**: Endothelium produces various inflammatory mediators and prevents inflammation.

**B. Regulation of blood pressure by vascular endothelial system**

Endothelial system plays an important role in short-term regulation of BP like baroreceptor reflex (Stauss HM & Persson PB., 2000). Normal levels of NO produced by endothelial cells is critical for the maintenance of basal vascular tone and BP (Jin RC & Loscalzo J., 2010).

The mechanism of regulation of blood pressure by endothelial system is as follows (Figure 4)

i. Elevation in BP increases vascular shear stress.

ii. Vascular shear stress, a mechanical stimulus causes an increase in concentration of cytosolic Ca$^{2+}$ in the endothelial cells.

iii. Ca$^{2+}$ binds with calmodulin and forms a Ca$^{2+}$-calmodulin complex. This complex increases the activity of endothelial isoform of nitric oxide synthase (eNOS).

iv. Nitric oxide produced by eNOS diffuses into the adjacent VSMCs and activates an enzyme guanylyl cyclase (paracrine effect).
v. Activated guanylyl cyclase increases the synthesis of 3,5-cyclic guanosine monophosphate (cGMP).

vi. cGMP reduces the intracellular (VSMCs) Ca\textsuperscript{2+} concentration.

vii. Reduction in intracellular Ca\textsuperscript{2+} concentration results in inhibition of Ca\textsuperscript{2+}-calmodulin myosin light chain kinase complex formation in the VSMCs promoting relaxation.

viii. Relaxation of VSMC decreases the vascular resistance, tone and thus reduces BP.

(Reference: Stauss HM & Persson PB., 2000)

**Figure 4** Mechanism of the vascular blood pressure control system

C. **Ageing and endothelial dysfunction**

Endothelial dysfunction is characterized by a shift of the normal endothelial function towards reduced vasodilation, a pro-inflammatory state and pro-thrombic properties (Endemann DH & Schiffrin EL., 2004). The age-related endothelial dysfunction associated with decreased bioavailability of NO contributes to increase in vascular tone, arterial
stiffness and hypertension (Matz RL et al., 2000; Torregrossa AC et al., 2011; Jin RC & Loscalzo J., 2010). A shift in endothelial function towards the vasoconstrictor dominance increases the peripheral vascular resistance, a pathognomonic characteristic of hypertension in the elderly (Figure 5). The endothelial-dependent vasodilator function is reduced with aging and this impaired NO-mediated vasodilatation is a potential contributor to the age-related increase in arterial stiffness and peripheral vascular resistance (Wilkinson IB et al., 2002; Fitch RM et al., 2001). Coronary endothelial dysfunction is an independent predictor of all-cause and CV mortality (Schachinger V et al., 2000; Suwaidi JA et al., 2000). It has been demonstrated that local arterial stiffness increases by blocking NO synthesis (Wilkinson IB et al., 2002) and removal of vascular endothelium in animal models (Boutouyrie P et al., 1997) indicating that endothelium derived NO contributes to the regulation of large artery stiffness in vivo.

2.5.3. Age-related changes in autonomic nervous system

The autonomic nervous system maintains vascular homeostasis through pressure, volume and chemoreceptor signals. The three endogenous catecholamines which play important roles in cardiovascular regulation are nor-epinephrine, epinephrine and dopamine.
The regulation of vascular resistance is also affected by age-related changes in the autonomic nervous system. An age-related increase in sympathetic nervous system activity has been demonstrated by higher plasma nor-epinephrine levels (Seals DR, Esler MD., 2000) and muscle sympathetic nerve activity (Malpas SC., 2010; Supiano MA., 2009). This rise in plasma nor-epinephrine levels with age is thought to be a compensatory mechanism for age-related decrease in beta-adrenergic response (Seals DR, Esler MD., 2000). Arterial baroreceptor sensitivity declines with age. This age-related decline in baroreceptor sensitivity leads to relatively greater activation of sympathetic nervous system (compensatory mechanism) for a given level of BP (Supiano MA., 2009).

Sympathetic nervous system maintains vascular tone. Its overactivity increases vascular tone, vascular stiffness and thus hypertension. Age-related arterial stiffness was shown to be associated with increased sympathetic activity in hypertensive (Mancia G et al., 1999) and also in healthy subjects (Dineno FA et al., 2000). Studies have also shown an association between increased sympathetic activity and endothelial dysfunction (Hijmering ML et al., 2002; Thijssen DHJ et al., 2006). Thijssen et al. demonstrated that sympathetic activation results in decrease in endothelial-dependent flow mediated dilatation (FMD) in superficial femoral artery in older persons and attenuation of this sympathetic activity restores the FMD (Thijssen DHJ et al., 2006).

2.5.4. Oxidative stress

Age-associated increase in oxidative stress has been implicated as one of the underlying causes of hypertension (Ceriello A., 2008; Mateos-Caceres PJ et al., 2012; Briones AM et al., 2010; Grossman E., 2008). An increase in production of ROS such as superoxide radicals (O$_2^-$), hydrogen peroxide (H$_2$O$_2$), hydroxyl radical (●OH) and singlet oxygen causes oxidative stress. Although ROS are generated in multiple compartments and by multiple enzymes within the cell, but the majority of ROS are produced within the mitochondria during ATP production by oxidative phosphorylation contributing to aging and age-related disorders. If ROS are not removed or neutralized, it can target various cellular constituents like lipid membranes, proteins, DNA and RNA. Our body has evolved complex antioxidant defense mechanism to prevent the deleterious effects of ROS. An imbalance between ROS and antioxidants results in oxidative stress (Kohen R et al., 2002). Oxidative
stress contributes to inactivation of NO resulting in its reduction in bioavailability and endothelial dysfunction (Schulz E et al., 2011; Silva BR et al., 2012). Endothelial dysfunction associated with decreased NO production results in impaired vasodilation and increased BP.

Reactive oxygen species influences cardiovascular structure and function by modulating cell growth and inflammatory responses via reduction-oxidation-dependent signaling pathways. Increased vascular oxidative stress damage the endothelium, reduces nitric oxide production by inhibiting eNOS pathways and impairs endothelium-dependent vasodilation with resultant enhanced vascular tone and thus hypertension (Briones AM et al., 2010; Grossman E., 2008). Further, oxidative stress causes thickening of the vascular media by promoting smooth muscle cell proliferation and hypertrophy with collagen deposition resulting in narrowing of vascular lumen (Grossman E., 2008; Schulz E et al., 2011). These evidences suggest that oxidative stress may play an important role in the development of hypertension.

### 2.5.5. Neurohormonal changes

Aging also declines the neurohormonal mechanisms such as the renin-angiotensin-aldosterone system and contributes to elevation in BP. In general, the elderly population has low levels of plasma renin activity, i.e. about 40%-60% of the levels found in younger individuals (Epstein M., 1996). This decreased plasma renin activity has been attributed to the effect of age-related nephrosclerosis on the juxtaglomerular apparatus (Lionakis N et al., 2000). Plasma aldosterone levels also declines with age. Age-related changes in kidney function associated with decreased ability to excrete sodium load may also contribute to an elevation of BP in elderly.

### 2.5.6. New molecular mechanisms associated with hypertension in elderly

The new proposed mechanisms involved in the development of hypertension in elderly are as follows (Figure 6):

a. Telomere shortening: Studies have shown a strong association between shorter telomere length and hypertension. Telomeres are the ends of the chromosomes that protect the end
growth of the chromosome from deterioration and preserve genomic integrity. The length of telomeres gets shortened progressively with replications. Growing evidence suggests that telomere shortening can be used as a marker of biological aging of the cardiovascular system and predictor for developing hypertension (Mateos-Caceres PJ et al., 2012).

b. Increase of deleterious micro particles: Small circulating procoagulant, prothrombotic and pro-inflammatory particles in plasma are called microparticles. These circulating microparticles are shed from the surface of different types of cells (platelet, leucocyte, erythrocyte and endothelial cells) in response to activation, injury and/or apoptosis. They are found associated with arterial thrombotic processes and increased in patients with hypertension. The deleterious effect of circulating microparticles on vascular function leads to endothelial dysfunction with impairment in NO production and release (Mateos-Caceres PJ et al., 2012).
c. Epigenetics and lifestyle: Epigenetics studies the interaction of DNA and its expression with the environment. Environmental factors such as diet, stress, obesity, smoking aging, and inactivity or sedentary lifestyle directly affect the incidence of hypertension (Mateos-Caceres PJ et al., 2012).

2.6. Pathologic consequences of hypertension in elderly

**Heart**: Cardiovascular disease is most common cause of death in hypertensive patients. Hypertension doubles the risk of coronary artery disease (CAD), ischemic heart disease (IHD), congestive heart failure (CHF) and peripheral arterial disease (PAD) (Figure 2). According to the American Heart Association Statistics Committee and Stroke Statistics Subcommittee, the prevalence of myocardial infarction was higher in elderly with hypertension than normal BP (Lloyd-Jones D et al., 2009). About 83% of deaths occurred due to CAD above 65 years of age (Franklin SS et al., 2001). Aortic stiffness is an independent predictor of CAD in patients with essential hypertension (Boutouyrie P et al., 2002). Active treatment leads to reduction in 25% of myocardial infarction and significant decrease in CHF (Supiano MA., 2009).

**Chronic Kidney disease**: Ageing is a risk factor for chronic kidney disease. Hypertension along with aging is a major risk for chronic kidney disease (CKD) (Figure 2). Systolic blood pressure is an independent predictor for CKD in elderly individuals with hypertension (Young AJH et al., 2002).

**Cerebrovascular disease**: In the elderly population, hypertension is a major risk factor for brain infarction and cerebral hemorrhage. The important component of BP related stroke risk is isolated systolic hypertension. Active treatment leads to reduction in 35% of stroke and significant decrease in dementia (Supiano MA., 2009). Systolic hypertension in elderly program (SHEP) has demonstrated that reduction of BP by active treatment resulted in reduction of incidence of both ischemic stroke by 37% and hemorrhagic stroke by 54% (Perry HM et al., 2000). Another study, The Systolic Hypertension in Europe Trial has also confirmed the stroke prevention by active treatment of ISH (PROGRESS Collaborative
Group., 2001). Age and hypertension are also an important risk factor for vascular dementia and Alzheimer’s disease (Rosendorff C et al 2007).

2.7. Diagnostic evaluation

Hypertension should never be diagnosed on the basis of a single measurement of BP. In the elderly population, the BP is more variable, so single measurement of BP leads to misdiagnosis of hypertension. A strong association between arterial stiffness and auscultatory gap has been noticed, especially in the elderly. Systolic BP is falsely increased by atherosclerotic and other vascular changes associated with age (Foran TG et al., 2004). As the measurement of BP depends on measuring on how much force it takes to compress an artery, so to compress the stiffened arteries the sphygmomanometer reading is falsely increased leading to false measurement of BP and misdiagnosis of hypertension. Hence, it has been recommended that the diagnosis of hypertension should be based on the average of a minimum of nine BP readings that have been measured on three separate visits (Supiano MA., 2009). More than 90% of older individuals suffer from essential hypertension. A diagnostic evaluation for finding the secondary causes for hypertension should be done as per the standard guidelines (The task force for the management of arterial hypertension of the ESH & ESC., 2007).

2.8. Management of Hypertension in elderly

There are evidences from the studies that lowering of BP in elderly hypertensive patients reduces CV morbidity and mortality. According the 2007 ESH/ESC Guidelines, the initiation of antihypertensive treatment should be based on the level of BP and total CV risk. When to initiate an intervention for blood pressure (life-style modality or antihypertensive intervention) has been summarized in Figure 7 (The task force for the management of arterial hypertension of the ESH & ESC., 2007). In general, the recommended target of treatment is to reach goal of SBP below 140 mmHg and DBP below 90 mmHg in hypertensive patients.
2.8.1. Non-pharmacological approach

Lifestyle modifications are widely accepted as a very important aspect not only for prevention of hypertension and CV risk but also for management of hypertension. It is to often overlooked in the management of hypertension in elderly. According to ESC/ESH 2007 guidelines, an appropriate lifestyle measures should be instituted in all patients, even with high BP including those who require drug treatment. The purpose of lifestyle changes is to control BP and CV risk factors, and to reduce number of doses of antihypertensive drugs. The recommendations as illustrated in Figure 7 are to begin with appropriate lifestyle modifications for upto 6-month period for Grade-I hypertension and for several weeks for Grade-II hypertension if not associated with any CV risk factors. In cases of Grade-I and II
hypertension with 1 or 2 CV risk factors then the intervention can be tried with life-style modality for several weeks. However, if life-style modality fails to reduce the BP to the level of recommended target then drug (antihypertensive) treatment can be commenced. Lifestyle changes should be used as an adjunctive, even if the drug therapy is needed (The task force for the management of arterial hypertension of the ESH & ESC., 2007).

The lifestyle modalities that are known to reduce BP or CV risk factors are smoking cessation, moderation of alcohol consumption, weight reduction in the overweight, reduction of salt intake, decrease in saturated and total fat intake, exercise, yoga, meditation and acupuncture. The JNC 7 gives an estimate of SBP changes for various lifestyle interventions. SBP decreases approximately by 5-20 mmHg per 10 Kg loss of weight in overweight, 2-8 mmHg by dietary sodium restriction, 4-9 mmHg by physical activity, 2-4 mmHg by moderate alcohol consumption and 8-14 mmHg by Dietary approaches to stop hypertension (DASH) diet (Chobanian AV et al., 2003).

The Trial of Non-pharmacologic Intervention in the Elderly (TONE) studied the effect of dietary sodium restriction, weight loss or combination of both in obese and non-obese patients with hypertension (BP<145/85 mmHg) while taking one antihypertensive. The participants were weaned from their antihypertensive drug with a goal of discontinuing the drug altogether following 90 days intervention (first session). The primary end points were the finding of elevated BP after drug weaning or discontinuation, the need to reinstitute antihypertensive therapy, CV events and death. The intervention led to fairly modest declines in dietary sodium (average of 40mmol/day) and body weight (average 3.5 Kg). About 40% participants did not experience a rise in BP and there was no need to reinivate antihypertensive therapy for about 30 months (Whelton PK et al., 1998).

A regular aerobic exercise for 30 min for 12 week program has lowered SBP by 8.5 mmHg, DBP by 5.1 mmHg and PP by 3.2 mmHg (Westhoff TH et al., 2007). Dietary modification is also an important lifestyle modality to lower BP in elderly. DASH diet with rich fruits, vegetables and low-fat dairy foods was shown as an effective and beneficial in Stage-1 Isolated systolic hypertension (Moore TJ et al 2001). In this study, Dash diet lowered SBP by 11.2 mmHg when compared to control group.
Yoga is emerging as an important lifestyle modality and physiological means for prevention and management of CV risk. Yoga is spiritually based, so elderly population may be more interested in practicing and following its lifestyle. It has many established health benefits. There are growing evidences that Yoga effectively controls hypertension and improves CV function (Refer section 5.3 for details).

2.8.2. Pharmacological approach

There are evidences from the studies that antihypertensive drug treatment in elderly patients benefitted in terms of reduced CV morbidity and mortality. A reevaluation of trials has found that no single trial has enrolled patients with Grade-1 hypertension. Results from meta-analysis of eight trials on elderly hypertensive patients has shown a reduction in total mortality by 13%, CV deaths by 18%, stroke by 30%, and coronary events by 23% following antihypertensive therapy (Staessen JA et al., 2000). The most common adverse effect caused by antihypertensive treatment is the development of postural hypotension. Therefore, it is recommended and important not to treat elevated BP too aggressively. The pharmacological drugs for hypertension in elderly with its main action and CV benefits are summarized in Table 7.

It has also been noticed that the elderly individuals suffering from isolated systolic hypertension are often resistant to pharmacological treatment, so any attempts to reduce the SBP aggressively lowers DBP (decreased with age) to such an extent to compromise coronary blood flow (Calhoun DA et al., 2008; Vongpatanasin W., 2014; Satoshkar RS et al., 2005). Aggressive approach to reduce the BP may also harm auto regulation of blood flow. Moreover, it has also been reported that arterial stiffness increases at a faster rate even in treated hypertensives with well controlled BP than in a normotensives (Benetos A et al., 2002). These reports indicate that an adequate approach that controls hypertension along with the progression of arterial stiffness with age is the need of the hour, in order to prevent the CV mortality and morbidity.
### Table 7 Pharmacological agents for hypertension: Main action and cardiovascular benefits

<table>
<thead>
<tr>
<th>Agent</th>
<th>Main action</th>
<th>Cardiovascular Benefits</th>
</tr>
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<tbody>
<tr>
<td>1. Thiazide (diuretic)</td>
<td>Inhibit reabsorption of sodium (Na(^+)) and chloride (Cl(^-)) ions from the distal convoluted tubules in the kidneys.</td>
<td>Reduces BP, Stroke &amp; CV mortality.</td>
</tr>
<tr>
<td>2. Angiotensin converting enzyme inhibitors (ACEIs)</td>
<td>Block the conversion of angiotensin I to angiotensin II.</td>
<td>Decreases systemic vascular resistance, BP, mortality in patients with MI and left ventricular dysfunction and progression of diabetic renal disease.</td>
</tr>
<tr>
<td>3. Angiotensin receptor blockers</td>
<td>Direct blockage of angiotensin II receptors</td>
<td>Causes vasodilation and decreases systemic vascular resistance, decreases secretion of vasopressin and aldosterone, lowers BP and stroke.</td>
</tr>
<tr>
<td>4. Calcium antagonists</td>
<td>Disrupts the movement of calcium through calcium channels in cardiac muscle and peripheral arteries.</td>
<td>Vasodilation and decrease in systemic vascular resistance, lowers BP, decreases CV complications in elderly patients with ISH.</td>
</tr>
<tr>
<td>5. β blockers</td>
<td>Lowers heart rate, decreases cardiac contractility and cardiac output, inhibit renin release, increase nitric oxide production, and reduces vasomotor tone.</td>
<td>Lowers BP</td>
</tr>
<tr>
<td>6. Other Agents:</td>
<td>Lowers BP</td>
<td></td>
</tr>
<tr>
<td>Renin inhibitors,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone receptor antagonists,</td>
<td></td>
<td></td>
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<tr>
<td>Centrally acting agents, direct</td>
<td></td>
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<tr>
<td>vasodilators</td>
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3. METHODS FOR ASSESSMENT OF ARTERIAL STIFFNESS

There are many invasive and non-invasive methods for the evaluation of arterial stiffness in the human beings.

3.1. Pulse pressure

Pulse pressure is a simple and best tool for measuring arterial stiffness and a good marker for CV risk in the elderly. Pulse pressure is an independent indicator of arterial stiffness. Studies have shown a positive correlation between PP and arterial stiffness (Safar ME., 2000; Safar ME et al., 2003; Cecelja M et al 2009). Systolic and diastolic pressure tends to increase with age up to 50-55 years. After 50-55 years, in most of the individuals the diastolic pressure falls and only systolic pressure rises with age thus causing widening of PP. Moreover, measurement of only PP is not adequate to assess arterial stiffness. Since age-related stiffness is greater in the aorta (elastic artery) than peripheral arteries, central aortic PP is a good marker than brachial PP to assess arterial stiffness.

Growing evidence suggests that PP is an important predictor of risk in elderly. Pulse pressure is more closely associated to CV events than SBP or DBP alone (Franklin SS et al., 2001). A meta-analysis of several studies with data of 8,000 elderly patients found that a 10mmHg increase in PP increased the risk of major CV complications and mortality by nearly 20% (Blacher J et al, 2000). Moreover, PP was an independent predictor of stroke and all-cause mortality in the SHEP study (Domanski MJ., 1999).

3.2. Pulse Wave velocity (PWV)

Pulse wave velocity measurement is the most simple, accurate and reproducible method for the assessment of regional arterial stiffness. It is the speed at which the forward pressure wave is transmitted from the aorta through the arterial tree (Mackenzie IS et al., 2002). It is widely used as an index of large artery elasticity and stiffness. PWV can be calculated in any segment of the circulation, provided the pulse waveform at two arterial sites is possible to record and time elapsed between the travels of waves and distance between them can be measured (Deloach SS & Townsend RR., 2008). There are various established methods for measuring PWV. The pulse waves can be recorded in different arteries using various sensors, transducers or probes, among which the most common are pressure sensitive transducers,
applanation tonometry (Nelson MR et al., 2002), Doppler ultrasound (Calabia J et al., 2011), piezoelectric transducers (Willum-Hansen T et al., 2006) and photoelectric transducers. The PWV of the given artery can be calculated by measurement of the transit time of the pulse waves ($\Delta t$) and the distance between two recording points ($d$) as follows:

$$\text{PWV (cm/m)} = \frac{\Delta t}{d}$$

The pulse transit time is the time taken by pulse wave to travel (between points) from peripheral wave to distal wave. The pulse transit time can be calculated by measuring time in seconds elapsed between the peak of the R-wave of ECG and the foot or onset of the pulse waves or between the foot of peripheral and distal wave (foot-foot method).

The PWV can be measured at different regions such as:
- Carotid- femoral PWV
- Carotid-radial PWV
- Femoral-tibial PWV
- Heart-brachial PWV
- Heart-ankle PWV
- Brachial-ankle PWV

Arterial stiffness increases with age due to decrease in elasticity and aorta is the major component of arterial elasticity. Hence, aortic PWV is the most preferred measure of arterial stiffness. The carotid-femoral PWV (c-f PWV) or aortic PWV is the gold standard method for assessment of aortic stiffness. Aortic PWV can also be measured non-invasively by using MRI. The accurate measurement of path length is an advantage of using MRI, however its usage is limited due to high cost and lack of availability (Mohiaddin RH et al., 1993). Brachial-ankle PWV (baPWV) was also shown as an independent predictor of carotid atherosclerosis in the elderly (Li JY & Zhao YS., 2010). The baPWV is strongly correlated with c-f PWV. Aortic stiffness is an independent predictor of all cause and CV mortality (Laurent S et al., 2001). It has been shown that, the aortic PWV is more predictive of CV mortality compared with PWV measured in the brachial or femoral circuits in end stage renal disease (ESRD) (Pannier B et al., 2005).
The determinants of the PWV are the elastic properties of the arterial wall, the geometry of the artery and the blood viscosity. Mathematically, Moens-Korteweg defined the PWV as follows (Bramwell JC, Hill AV., 1922):

\[
PWV = \sqrt{\frac{Eh}{2\rho r}}
\]

Where \(E\) is Young’s elastic modulus in the circumferential direction, \(h\) is the wall thickness, \(r\) is the radius of the vessel and \(\rho\) is the blood density. Moens-Korteweg equation can be used to calculate the PWV.

### 3.3. Arterial distensibility and compliance

The change in diameter of an artery in relation to distending pressure provides a direct measure of arterial stiffness. Distensibility and compliance of a number of arteries such as carotid, brachial, radial and aorta can be assessed. To evaluate these parameters, the diameter of the artery and its pressure is required to be measured. Ultrasound is commonly used imaging technique to measure the arterial diameter. While evaluating the local arterial stiffness of carotid or aorta, brachial BP is most frequently used, assuming that the BP of the aorta and carotid arteries is similar to the brachial artery (Rhee MY et al., 2008). There are conflicts on whether local arterial stiffness reflects the stiffness of other arteries.

### 3.4. Stiffness index and Reflection index

Stiffness index and reflection index (RIx) reflects systemic arterial stiffness. They are usually measured from the digital volume pulse waveform recorded using Finger Photoplethysmograph (Mackenzie IS et al., 2002).

Reflection index reflects the peripheral vascular tone. A comparative study revealed that pulse wave velocity correlated more closely with the expected influences on vascular compliance (age and atherosclerosis) than photoplethysmography of the digital volume pulse.

### 3.5. Arterial stiffness index

Arterial stiffness index is estimated by quantifying the oscillometric envelopes derived from the oscillations in the respective artery (Naidu MUR et al., 2012).
3.6. **Systemic arterial compliance**

Arterial compliance is defined as the relationship between the change in volume and the change in the distending pressure. The simplest method to measure systemic arterial compliance is the ratio of the stroke volume (SV) to the pulse pressure (PP).

\[
\text{Compliance} = \frac{SV}{\Delta P}
\]

The stroke volume can be measured invasively or non-invasively (Rhee MY et al., 2008). Brachial BP is most frequently used, assuming that the Central PP is similar to the brachial artery. Most of the investigators assess the carotid and aorta BP with applanation tonometry using a transfer function. Other method is ‘area method’ for measuring systemic arterial compliance.

3.7. **Augmentation index (AIx)**

The arterial pulse wave is composed of a forward pressure wave that arises from the left ventricular output and a backward pressure wave (wave reflection) reflected from the point of impedance mismatch (arterioles). Though, there are many reflection points in the body at various distances from the heart, the reflected waves act like a single wave arising from one functional reflection point. The velocity of pressure wave along the arterial depends on the elasticity of the vessel wall. More the stiffness (less elasticity), higher is the velocity. Normally, the wave reflection arrives at the aortic root during diastole which augments the diastolic pressure and enhances the myocardial perfusion. In the stiffened arteries, the pressure wave travels at high speed along the arterial tree and reflected wave arrives earlier during systole, when the ventricle is still ejecting blood, adding the reflected wave to the forward wave resulting in augmentation of the central systolic pressure. Early arrival of reflected wave during systole leads to decrease in diastolic pressure causing reduction in myocardial perfusion. The rise in the systolic pressure is called an augmentation pressure. The aortic AIx is the ratio of augmentation pressure to the aortic PP and is expressed in percentage. So, the AIx is a simple method to measure the wave reflection, which reflects the arterial stiffness. More the stiffness, higher is the augmentation index (Rhee MY et al., 2008; Mackenzie IS et al., 2002; Laurent S., 2006).
4. METHODS FOR EVALUATING ENDOTHELIAL FUNCTION

There are many established invasive and non-invasive methods for the evaluation of endothelial function in the human beings.

4.1. Flow mediated dilatation

Conduit vessels respond to increase in blood flow (shear stress) by increasing vessel diameter. This phenomenon of vasodilation in response to alterations in blood flow is called as flow-mediated dilatation (FMD). Flow-mediated dilatation is endothelial dependent and is mainly mediated by endothelial-derived NO (Lekakis J et al 2011).

The FMD technique measures changes in conduit artery (mostly brachial artery) diameter by ultrasound in response to two stimuli: endothelial-dependent stimulus (shear stress) and endothelial-independent stimulus (Nitroglycerine). The vasodilation response to the shear stress reflect local bioactivity of endothelial-derived NO while to the nitroglycerine reflect vascular smooth muscle function (Corretti MC et al., 2002). Due to its non-invasive nature and reliability, it is widely used in the study of endothelial physiology. But, to obtain accurate and reproducible measurements, highly trained operators are most essential.

4.2. Coronary endothelial function

Coronary endothelial function can be assessed by both invasive and non-invasive techniques. Quantitative Coronary angiography (QCA) is an invasive technique that measures changes in the epicardial coronary arteries diameter in response to the pharmacological stimuli such as intracoronary infusion of endothelial agonists (acetylcholine, metacholine or papaverine) and vascular smooth muscle relaxants (nitroglycerine). Non-invasive methods have been developed to assess coronary endothelial function using computed tomography (CT) (Husmann L et al., 2008) imaging or magnetic resonance imaging (MRI) (Terashima M et al., 2008).
4.3. Venous occlusion Plethysmography

This is the oldest method (established more than 100 years ago) used to assess the blood flow in humans. Venous occlusion plethysmography (VOP) is an invasive technique to assess endothelial function. It is based on the measurement of tissue (usually muscular) blood flow by the assessment of the tissue volume change. Strain-gauge technique is a highly reproducible and minimal invasive VOP method that is applied in the forearm to investigate in vivo endothelial function in the human microcirculation. This technique requires brachial artery cannulation for intra-arterial infusion of endothelial agonists and vascular smooth muscle factors in order to assess endothelial-dependent and independent vasodilation respectively (Lekakis J et al., 2011).

4.4. Pulse wave analysis

Endothelial function can be assessed by quantifying the changes in waveform (pressure waveform or digital volume pulse waveform) in response to the endothelial-dependent agonist (salbutamol) and vascular smooth muscle dilators. The arterial pulse wave or digital volume pulse is composed of a forward pressure wave that arises from the left ventricular output and a backward pressure wave (wave reflection) reflected from the point of impedance mismatch (mainly arterioles). This waveform contains important information about the arterial stiffness and endothelial function.

Wave reflection can be quantified by determining AIx or RIx, which represents the difference between the first and second systolic peaks (Chowienczyk PJ et al 1999). Impedance of the small arteries and arterioles depends to a large extent on smooth muscle tone which is mainly mediated by endothelium-derived NO. Thus, changes in small artery or arteriole tone affect wave reflection, so vasodilation reduces AIx or RIx while vasoconstriction increases them (Lekakis J et al., 2011).

4.5. Peripheral arterial tonometry

Recently, a simple, non-invasive technology based on measurement of peripheral vasodilator response at fingertip to reactive hyperaemia induced by temporary arterial
occlusion (digital reactive hyperaemia) known as peripheral arterial tonometry (EndoPAT) has been developed to assess peripheral vascular endothelial function (Kuvin JT et al., 2003).

4.6. Laser Doppler flowmetry

This technique is based on monitoring of skin microvascular blood flow with the assumption that the response noticed in the cutaneous circulation is a window towards the responses that should be observed in other vascular beds (Lekakis J et al., 2011). Laser Doppler flowmetry measures the changes in skin blood flow in response to the acetylcholine (endothelial agonist) delivered through iontophoresis or micro-dialysis, post-occlusive hyperaemia or local skin heating.

4.7. Biochemical markers

The biomarkers used to examine endothelial function are plasma asymmetrical dimethylarginine (ADMA) concentrations, oxidized low-density lipoprotein, vascular cell adhesion molecular (VCAM)-1, intercellular adhesion molecule (ICAM)-1, endothelial leucocyte adhesion molecule (ECAM)-1, total serum nitric oxide concentration and eNOS activity (Burger D & Touyz RM., 2012; Lekakis J et al., 2011).
Chapter II Review of Literature

5. YOGA

5.1. Introduction

Yoga is an ancient system having a psycho-somatic discipline, comprising physical and mental techniques that help to achieve a harmony between our mind and body. It is a tradition of lifestyle, health and spirituality. The term ‘Yoga’ is derived from Sanskrit word ‘Yuj’ which means joining. It is joining of individual self with universal self. Yoga is a conscious process of gaining mastery over the mind. It is a special skill to calm down the mind. According to Swami Vivekananda, yoga is a means of compressing one’s evolution into a single life or a few months or even a few hours of one’s bodily existence. Sri Aurobindo considers it as a means for self-perfection (Nagendra HR., 2004).

Yoga is originated in India and has a history of about 5000 years. Its roots are found in the Vedic period. After the period of Vedas, one of the great Seers, Maharishi Patanjali systematized yoga by compiling the essential features and principles of Yoga in the form of aphorisms (Sutras) about 5000 years ago. ‘Yoga Sutra’ was the text written by Maharishi Patanjali on classical yoga, the origin of which is estimated to date back to the period between 200 BC and 300 AD. After Maharishi Patanjali, many seers have contributed for the development of Yoga worldwide. Yoga includes diverse practices such as maintenance of posture (asanas), breathing practices (Pranayama), spiritual lectures, and meditation including prayer and devotional songs.

5.2. Streams of Yoga

There are four streams of yoga. They are as follows

i. Jnana Yoga

Jnana Yoga is the yoga of knowledge. Jnana is the Sanskrit word which means ‘knowledge’. It is a means to inquire into its own nature. Yoga practitioner (Yogi) uses his mind to inquire into its own nature. It sharpens the mind and helps to discriminate between the real and the unreal, the permanent and the transitory.
ii. Bhakti Yoga

Bhakti Yoga is the science of emotion culture. It is the path of worship. This path of worship is a boon to gain control over emotional instabilities by properly harnessing the energy involved in it. This path overcomes our selfishness, hatred, greed, jealousy and raises us to the highest levels of universal brotherhood and oneness. In the path of workship or bhakti, we surrender in total ourselves physically, mentally and intellectually.

iii. Karma Yoga

Karma Yoga is the path of work or action. It involves doing action selflessly without thought of gain or reward. By detaching ourselves from the fruits of our actions and offering them up to God, we learn to sublimate the ego. Bhagavad Gita defines as “Karma Yoga is the selfless devotion of all inner as well as the outer activities as a sacrifice to the Lord of all works, offered to the eternal as master of all the soul’s energies and austerities”.

iv. Raja Yoga

Raja Yoga is the path of will power. It is the science of physical and mental control. Raja Yoga is a conscious process of gaining mastery over the mind. It is based on Astanga Yoga (referring to the eight limbs) described in Yoga Sutras by Maharishi Patanjali. One can reach to the higher states of consciousness through eight limbs of Astanga Yoga. They purify the body and mind. The eight limbs are broadly divided in two categories: Bahiranga Yoga (used for indirect control of mind) and Antaranga Yoga (mind is used directly for culturing itself). They are summarized in Table 8.

5.3. Yoga and cardiovascular health

Yoga has many established health benefits and is emerging as an important lifestyle modality for prevention and management of CV risk. Yoga has been shown to control hypertension and improves CV function in middle-aged subjects (Selvamurthy W et al 1998; Murugesan R et al., 2000; Anand MP., 1999; Bharshankar JR et al., 2003). A meta-analysis of 3168 participants showed evidence for clinically important effects of yoga
### Table 8 Eight limbs of Astanga Yoga

<table>
<thead>
<tr>
<th>No.</th>
<th>Limbs</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1.  | Yama  | Set of prohibitions or Don’ts to gain mastery over mind:  
|     |       | - Ahimsa or non-violence (absence of violence),  
|     |       | - Satya or truth (not to speak untruth),  
|     |       | - Asteya or non-stealing (not to steal),  
|     |       | - Brahma or control of all senses  
|     |       | - Anupagraha or non-possession.  |
| 2.  | Niyama | A set of Do’s:  
|     |       | - Saucha or purity- this internal and external cleanliness.  
|     |       | - Santosha or contentment  
|     |       | - Tapas or austerity  
|     |       | - Swadhyaya or study of the sacred texts  
|     |       | - Ishwara Pranidhana which is constantly living with an awareness of the divine Presence (surrender to God's Will).  |
| 3.  | Asana | Yoga postures |
| 4.  | Pranayama | Regulation or control of the breath. |
| 5.  | Pratyahara | Mastery through senses- withdrawal of the senses in order to still the mind. |
| 6.  | Dharana | Concentration, focusing of mind or fixing the mind on an object. When dharana is achieved it leads to the next step. |
| 7.  | Dhyana | Meditation: is that state of pure thought and absorption in the object of meditation. There is still duality in Dhyana. When mastered Dhyana leads to the last step: |
| 8.  | Samadhi | The super conscious state. In Samadhi non-duality or oneness is experienced. This is the deepest and highest state of consciousness where body and mind have been transcended and the Yogi is one with the Self or God. |
on CV risk factors and suggested that yoga can be considered as an ancillary intervention for patients with or without CV risk (Cramer H et al., 2014).

Recently, a systematic review (6 studies involving 386 patients) on effect of yoga on essential hypertension shown yoga as an effective modality for lowering BP. The studies included in this review were having a wide variation in the age of subjects from 20-75 years and total duration of intervention ranged from 6 to 12 weeks (Wang J et al., 2013). They reported that yoga significantly lowered SBP (-2 to 29.17) and DBP (-0.74 to -23.67) when compared to conventional treatment or no treatment.

The mechanism of yoga-induced BP reduction in young and middle-aged subjects may be attributed to its beneficial effects on the autonomic neurological function. Various studies have shown that yoga significantly modulates the autonomic nervous system activity. Yoga practice and meditation reduces sympathetic activity and shifts the autonomic balance towards the parasympathetic dominance (Patil SG et al., 2013; Pal GK et al., 2013). Yoga based meditation was also shown to reduce sympathetic activity and increase vagal tone (Pailoor S et al., 2009). Restoration of baroreflex sensitivity (decreased in in patients (middle-aged) with essential hypertension following yoga practice has been reported (Selvamurthy W et al 1998). Recently, we have reported a significant reduction in SBP, DBP and PP following yoga practice in elderly with grade-I hypertension (Patil SG et al., 2014). The mechanism of yoga-induced regulation of BP remains unknown and has to be determined.

There are conflicting results on yoga effects on vascular function. In a cross-sectional study, Duren CM et al. demonstrated a lowering effect of yoga on arterial stiffness in healthy subjects aged between 40 and 65 years (Duren CM et al., 2008). In this study, Yoga group subjects performed yoga at least 2 days a week in the previous year (n=8) and aerobic group subjects performed aerobic exercise for three or more days a week for at least 30 minutes a day for the last year (n=10). In contrast, Hunter SD et al. did not find any significant changes in the arterial stiffness in the yoga practitioners (Hunter SD et al., 2013). This study assessed arterial stiffness in healthy middle-aged and older subjects in two settings: a cross sectional (n=34) and interventional (n=13). They have given 12 weeks of Hatha yoga intervention for sedentary subjects.
However, we could not find any randomized controlled studies that assessed the effect of yoga on vascular stiffness, especially in elderly population with CV risk.
6. REFERENCES

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