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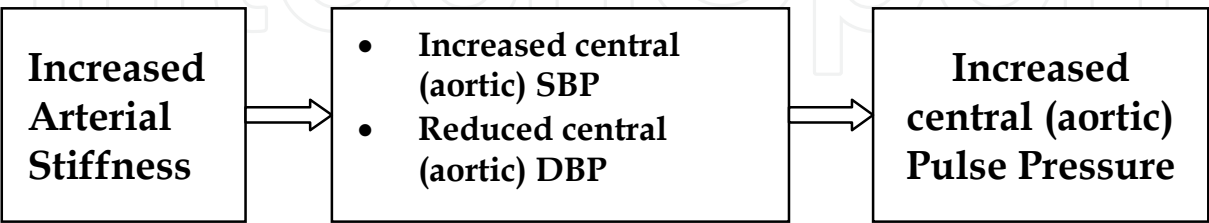
Pulse Pressure and Target Organ Damage

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1. Introduction

Hypertension remains the major risk for cardiovascular disease, stroke and end-stage nephropathy. Hypertension is traditionally defined in terms of elevated systolic and or diastolic blood pressure (BP). Recently, however, there has been increased recognition of the importance of high brachial pulse pressure (PP) as an important and independent predictor of increased cardiovascular morbidity and mortality, especially in senior subjects (Franklin et al., 2001). This paradigm shift is attributed to the aging of the population. The aging process is associated with an increased incidence of systolic hypertension, and in particular isolated systolic hypertension (ISH) (Franklin et al., 1999; Franklin et al. 2001; National High Blood Pressure Education Program Working Group, 1994). Both systolic and isolated systolic hypertension are characterized by wide (high) PP (Franklin et al. 2001 & National High Blood Pressure Education Program Working Group, 1994).

Increased pulse pressure (PP) defined as the difference between inappropriately elevated systolic blood pressure (SBP) and reduced diastolic blood pressure (DBP) at any value of mean arterial pressure (MAP) is a surrogate measure of increased arterial stiffness of central elastic arteries (aorta and its major branches) (Figure 1) (Dart & Kingwell, 2001; Safar et al., 2003). Arterial stiffness has emerged as an important independent predictor of adverse cardiorenal outcome in the general population (Figure 2) (Boutouyrie et al., 2002). Central PP is considered an accurate indicator of arterial stiffness (Boutouyrie et al., 2002). However, brachial PP is a widely accepted marker of arterial stiffness in the elderly and in some middle-aged individuals because central PP equalizes brachial PP during aging due to PP augmentation by early wave reflection (Dart & Kingwell, 2001).

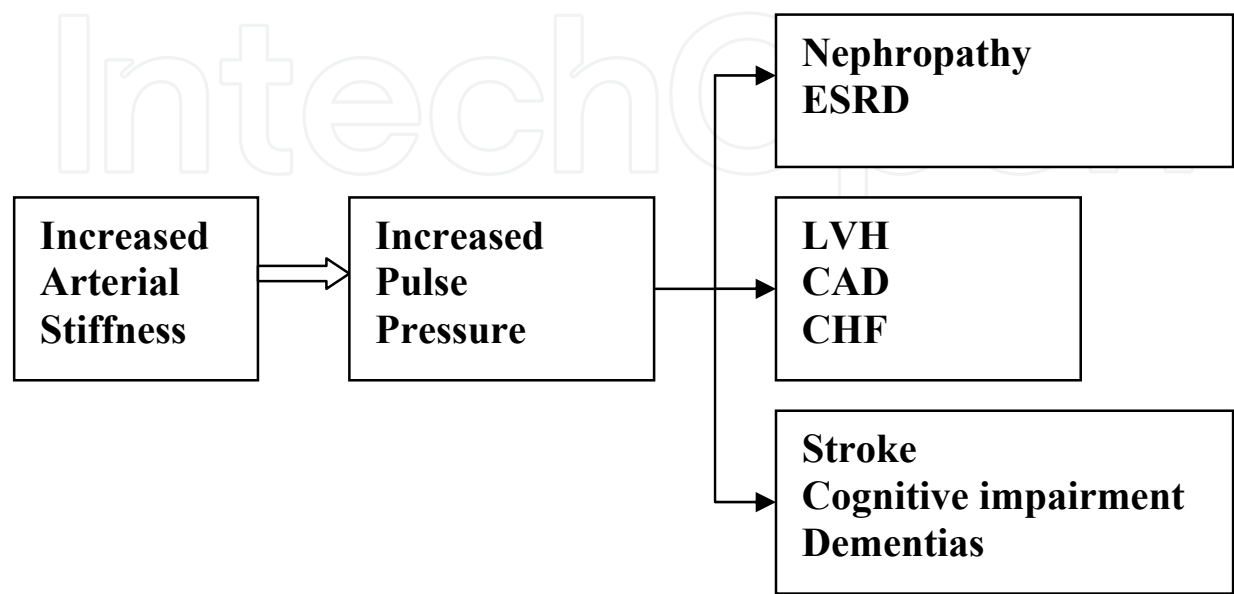


SBP= Systolic blood pressure, DBP= Diastolic blood pressure

Fig. 1. Determinants of Central Pulse Pressure

The relationship between PP and age is reported to be J-shaped, negative in subjects younger than 50 years and becoming positive after the age of 50 years. These findings suggest different

pathophysiologic implications in younger versus older subjects. In subjects younger than 50 years of age, with preserved left ventricular dynamics, PP is related to a hyperdynamic cardiovascular state whereas, after the age of 60 years, arterial stiffening becomes a major determinant (Wilkinson et al., 2001). In fact, after the age of 60 years, the increase in PP results both from continuous elevation in SBP and a decrease in DBP (Franklin et al., 2001).



LVH= Left ventricular hypertrophy, CAD= Coronary artery disease, CHF= Congestive heart failure, ESRD= Endstage renal disease

Fig. 2. Relationship between increased arterial stiffness, increased pulse pressure and target organ disease

Several observational and clinical studies have indicated that, in both normotensive and hypertensive middle-aged and older subjects, wide PP is a better predictor of cardiovascular events and target organ disease than increased SBP and MAP adjusted for age, sex and other cardiovascular risk factors (Franklin et al., 2001). Further, a level of PP that predicts cardiovascular events in hypertensive patients appears to be equal or greater than 60-63mmHg (De Simone et al., 2005).

An increased brachial PP is an independent predictor of cardiovascular mortality not only in hypertensive men but also in normotensive men aged 40-69 years (Benetos et al., 1998). Thus, normotensive men with PP > 55mmHg were shown to have a 40% increased cardiovascular risk compared to normotensive men with same age but PP< 45mmHg (Benetos et al., 1998). Further, the predictive value of PP was observed even in well controlled hypertensive subjects (Benetos et al., 1998). Finally, the predictive power of PP has been demonstrated in subjects with evidence of other target organ involvement such as left ventricular dysfunction, endstage renal failure and in those with diabetes mellitus (Schram et al., 2002).

In contrast, in subjects younger than 50 years, brachial PP is not associated with a poor prognostic implication. In these subjects, the central arteries are more distensible and velocity of reflected pulse wave is low (Kotsis et al., 2011). As a result, SBP and PP increase

significantly by about 12-14mmHg from central to peripheral arteries. This is known as the amplification phenomenon (Franklin et al., 2001 & Karamanoglu et al., 1993). Central and peripheral MAP and DBP, however, are not significantly different. Consequently, the peripheral (brachial) SBP and PP overestimate central (aortic) values (Franklin et al., 2001 & Karamanoglu et al., 1993). After the age of 55-60 years, as a result of arterial aging, central SBP and PP may increase even more than peripheral pressures. As a result, central SBP and PP become equal to or higher than peripheral (brachial) SBP and PP (Figure 3) (Franklin et al., 2001; Karamanoglu et al., 1993; Kotsis et al., 2011).

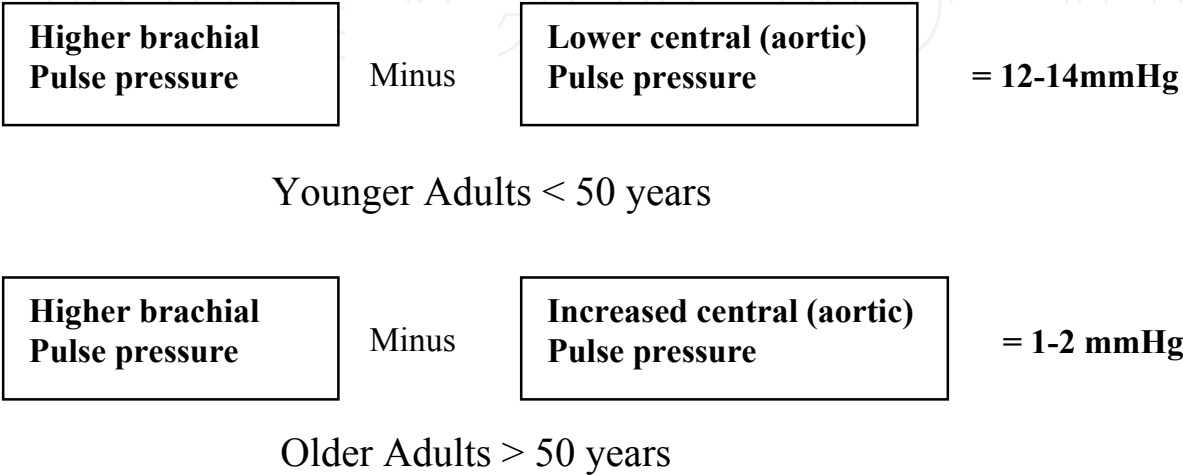


Fig. 3. Amplification phenomenon in younger and older adults

2. Genesis of the pulse pressure

The various BP components in the systemic circulation are the resultant of an interaction between left ventricular outflow (ejection) and properties of the large arterial system (aorta and its proximal major branches) (Benetos et al., 2010 & Van Bortel et al., 2001).

Ejection of blood from the left ventricle (LV) generates flow and pressure waves (Safar et al., 2003 & Wilkinson et al., 2001). The pressure wave generated by the LV travels down the arterial tree and is reflected back at any discontinuity of the arterial wall, namely at the multiple resistance arterioles and their bifurcation (Safar et al., 2003). The pressure waveform recorded at any site of the arterial tree is the sum of a forward traveling waveform, the incident pulse wave generated by left ventricular ejection and a back travelling wave, the reflected pulse wave (Safar et al., 2003 & Wilkinson et al., 2001).

2.1 Youth and early adulthood

In youth and early adulthood, the peak pressure recorded in the proximal aorta during LV ejection represents the SBP. Due to high distensibility of the system, the pressure wave form travels at low velocity (low pulse wave velocity- PWV) to the periphery and the reflected wave returns to the heart after closure of the aortic valve, so that it does not create an additional pressure load to the contracting LV (Safar et al., 2003). It does, however, increase the pressure during early diastole thereby enhancing DBP and improving coronary perfusion (Safar et al., 2003).

PP which represents pressure fluctuations resulting from episodic cardiac contraction is approximately 25mmHg in the aorta and is amplified to 40mmHg in the brachial and radial arteries.

2.2 Aging

In humans, the aging process is associated with structural and functional changes in the aorta and proximal elastic arteries. These vessels dilate and stiffen.

With increased arterial stiffness, the pulse wave travels faster, and reflected pulse wave merges earlier with the incident wave, augmenting aortic systolic blood pressure, rather than diastolic blood pressure (Safar et al., 2003 & Wilkinson et al., 2001). As a result, left ventricular load is increased and coronary perfusion is compromised (Safar et al., 2003 & Wilkinson et al., 2001).

3. Amplification phenomenon

BP amplification is defined as the elevation of PP from the central aorta towards the periphery and is mainly attributed to an increase in SBP (Benetos et al., 2011; McEniery et al., 2005). Pressure wave amplification can be explained by the reflection phenomenon of the oscillating BP wave (Benetos et al., 2011; McEniery et al., 2005). In the presence of compliant (i.e. low stiffness) central elastic arterial system as in young adults, PWV is low, the reflected pulse wave will attain the peripheral arteries (i.e. radial arteries) during systole due to their proximity to the reflecting sites, and the central arteries during the diastolic period (Benetos et al., 2011). This mechanism explains PP phenomenon namely why the peripheral (brachial, radial) is higher than the central (aortic) PP. The ratio of brachial / central PP varies from 70% in subjects younger than 20 years to 20% in those older than 80 years (McEniery et al., 2005). When expressed in absolute change in mmHg, the difference between brachial and central PP varies from 20 to 7 mmHg (Benetos et al., 2011; McEniery et al., 2005). Loss of PP amplification, associated with an increase in central PP and PWV have been shown to be significant predictors of all cause and cardiovascular mortality (Benetos et al., 2010).

3.1 Determinants of PP amplification

Several factors have been postulated to alter PP amplification including aging, gender, and traditional risk factors (McEniery et al., 2005).

In youth and early adulthood, PP increases significantly from central (aorta / proximal elastic arteries) to peripheral (brachial) arteries, leading to PP amplification. This phenomenon is attributed to higher SBP and slightly lower DBP in peripheral (brachial, radial) arteries. In contrast, MAP gradient between central and peripheral arteries is only 1-2mmHg.

In middle-aged and elderly subjects, the increasing stiffness of central elastic arterial system is associated with elevation of central SBP, reduction in DBP, widening of central PP and loss of PP amplification.

Females have a lower PP amplification than males of similar age which is attributed to:

- i. i) shorter arterial tree;
- ii. ii) additional gender related factors.

Subjects with hypertension, diabetes, dyslipidemia or established CV disease tend to have a low PP amplification independent of age, height or gender.

Age and gender remain the major determinants of PP amplification.

4. Kidney damage and pulse pressure

It is well established that hypertension and chronic kidney disease (CKD) are closely linked. Hypertension is the second most common primary diagnosis in patients with incident or prevalent endstage renal disease (ESRD). Further, most forms of CKD are etiologically related to hypertension (Udani et al., 2011). In addition, coexistent or superimposed hypertension is the major risk for progression of CKD (Hsu et al., 2005; Perry et al., 1995; Udani et al., 2011). The rates of CKD and ESRD in the USA attributed to hypertension have been steadily increasing partly attributed to the aging process (Udani et al., 2011).

Epidemiologic data and several clinical studies have documented a graded relationship between degree of BP elevation and renal functional impairment. Malignant hypertension, characterized by marked BP elevations (SBP/DBP \geq 220/120mmHg) leads, if untreated, to severe renal damage and irreversible renal failure which is attributed to occlusive intra-renal arterial and arteriolar lesions (Bidani and Griffin, 2004). Conversely, data from several cohort studies provide strong support for nonmalignant hypertension as a causal risk for development of CKD and endstage renal failure (ESRD). In 12000 hypertensive patients from multiple Veterans Administration Centers followed up for 15 years, Perry et al. reported that uncontrolled hypertension was associated with a risk for development of CKD/ESRD (Perry et al., 1995). Specifically, the risk ratio for CKD was 2.8 for a pre-treatment SBP= 166-180mmHg, and 7.6 for a pre-treatment SBP>180mmHg (Perry et al., 1995).

Even modest BP elevation in the non-hypertensive range appears to confer increased risk of CKD. Compared to BP< 120/80mmHg, the adjusted risk ratio for developing ESRD was 1.62 for BP=120-129/80-84 mmHg and 1.98 for BP=130-139/84-89 mmHg in a cohort of 316675 adult members of the Kaiser Permanente of Northern California (Hsu et al., 2005).

4.1 Hypertensive nephropathy

4.1.1 Histopathologic patterns

Hypertension-induced kidney damage can be classified into two clinical and histopathologic patterns: 1) vascular, 2) glomerular.

The vascular pattern, often referred as nephrosclerosis can be further subdivided into two forms – namely benign and malignant nephrosclerosis (Bidani and Griffin, 2004). Benign nephrosclerosis, the most frequent form which occurs in the majority of patients with essential hypertension, is characterized by hyaline arteriosclerosis which is slowly progressive but does not compromise the vascular lumen (Bidani and Griffin, 2004). Accordingly, significant loss of nephrons and compromise of renal function are infrequent (Bidani and Griffin, 2004). In contrast, malignant hypertension is characterized by marked

BP elevation (SBP/DBP \geq 220/120 mmHg) and occlusive arterial and arteriolar preglomerular lesions with prominent fibrinoid necrosis leading to ischemic glomerular injury (Bidani and Griffin, 2004). Rapid deterioration of renal function and irreversible renal failure can develop in the absence of adequate BP reduction (Bidani and Griffin, 2004). However, with the availability of effective modern antihypertensive therapy, malignant hypertension has become an uncommon cause of ESRD.

The glomerular pattern, characterized by an accelerated segmental or global glomerulosclerosis, is an increasingly recognized lesion of hypertension-induced kidney damage (Bidani and Griffin, 2002 & Bidani et al., 2009). It is often superimposed on the underlying primary nephropathy and occurs even with mild to moderate BP elevations. Further, these histopathologic renal changes are independent of presence of nephrosclerosis (Bidani and Griffin, 2002 & Bidani et al., 2009). In fact, vascular lesions are not prominent.

4.1.2 Mechanisms of hypertension-induced nephropathy (CKD)

The mechanisms of hypertension-induced renal injury and appearance of hypertensive nephropathy have not been completely elucidated. A growing body of evidence suggests a link between aortic stiffness and renal function (Mimran, 2006). Aortic stiffness causes increased SBP and wide (increased) PP, both factors associated with increased rates of decline in renal function and progression to renal impairment (Mimran, 2006).

4.2 Renal autoregulation

Disturbances in the mechanisms of renal autoregulation appear to play important roles in the appearance and progression of hypertensive nephropathy (Loutzenhiser et al., 2006).

One of most striking features of the renal circulation is the phenomenon of autoregulation by which the kidney maintains constant renal blood flow (RBF) and glomerular filtration rate (GFR) in the face of wide fluctuations of systemic BP (Loutzenhiser et al, 2002). This dual regulation of both RBF and GFR is achieved by proportionate changes in the tone of the preglomerular and postglomerular resistances (Loutzenhiser et al, 2002). This process is initiated by combination and integration of two mechanisms, the faster renal myogenic response and the slower tubuloglomerular feedback (TGF) system (Loutzenhiser et al, 2002). TGF involves a flow-dependent signal that is sensed at the macula densa and alters the tone of the adjacent preglomerular and postglomerular resistances (Loutzenhiser et al, 2002). The renal myogenic response involves a direct vasoconstriction of the afferent arteriole when this vessel is exposed to an increase in transmural pressure (Loutzenhiser et al, 2002, 2006).

By using the hydronephrotic rat kidney preparation, Loutzenhiser et al reported that the myogenic response is influenced only by the SBP, even when MAP is kept constant (Loutzenhiser et al, 2002, 2006).

Normally, increases in systemic BP, whether sustained or intermittent are prevented from fully reaching the renal microcirculation by proportionate vasoconstriction of the preglomerular afferent arterioles (Loutzenhiser et al, 2002, 2006). Systolic BP and PP appear to be the major determinants of the tone of the afferent arterioles, independent of MAP and DBP (Loutzenhiser et al, 2002, 2006). In fact, recent clinical studies indicate that hypertensive

renal injury correlates most strongly with SBP and PP (Ford et al., 2010; Mimran, 2006; Safar, 2004; Verhave et al., 2005).

In contrast to the microcirculation of other organs, the renal microcirculation presents two special features. First, glomerular MAP and pulsatile pressures are high, representing about 60% of the aortic pressures (Mitchell, 2004). Second, because the resistance is higher in the efferent arteriole than in the afferent arteriole, the pressure drop across the afferent arteriole is low (Mitchell, 2004). These hemodynamic characteristics allow the maintenance of glomerular filtration but expose the glomerular microcirculation to high pressure injury and biotrauma (Mitchell, 2010). Under normal conditions, the renal myogenic response prevents transmission of the elevated MAP and pulsatile pressure from reaching the glomerular capillaries (Loutzenhiser et al, 2002).

Renal autoregulation mediates hypertension-induced nephropathy (CKD) by 2 mechanisms: i) intact renal autoregulation associated with elevated systemic BP levels within or beyond the autoregulatory threshold; ii) impaired renal autoregulatory process.

4.2.1 Intact renal autoregulation

4.2.1.1 Elevated systemic BP levels within the autoregulatory threshold

In mild to moderate uncomplicated essential hypertension, the renal autoregulatory mechanisms are intact and BP levels remain within the autoregulatory threshold (Bidani & Griffin, 2002, 2004). The elevated systemic BP enhances the myogenic tone of the afferent arteriole, preserving the relative constancy of the glomerular capillary hydrostatic pressures and insulating the renal microcirculation from biotrauma (Bidani & Griffin, 2002, 2004). Renal functional impairment is minimal and development of CKD and ESRD is infrequent (Bidani & Griffin, 2002, 2004). However, prolonged exposure of the renal circulation to elevated systemic BP levels may initiate the pattern of benign nephrosclerosis in the afferent arterioles which is characterized by vascular lesions of nonspecific hyaline arteriosclerosis (Bidani & Griffin, 2002, 2004).

4.2.1.2 Elevated systemic BP beyond the autoregulatory threshold

In contrast, in malignant hypertension, although the autoregulatory process is still preserved, the markedly elevated MAP levels, which exceed the upper threshold of the process, may cause severe renal vascular and glomerular disruptive lesions, resulting in severe renal functional impairment (Bidani & Griffin, 2002, 2004). However, with the advent of renal vascular disease, renal autoregulatory responses may become secondarily impaired leading to amplification of the renal damage.

A sudden severe BP elevation is much more likely to exceed the autoregulatory threshold than a progressive rise in BP to the same levels. This is due to the protection afforded by the rightward shift of the upper and lower limits of autoregulation, a characteristic feature in chronic hypertension (Bidani & Griffin, 2004).

4.2.2 Impaired renal autoregulation

Impaired renal autoregulation is frequently reported in states such as diabetes and CKD (Bidani & Griffin, 2004). This hemodynamic alteration tends to be manifested as dilatation of

the afferent arteriole, glomerular hypertrophy, hyperfiltration injury and subsequent extracellular matrix production and glomerulosclerosis with irreversible reduction in GFR (Bidani & Griffin, 2004). In addition, increased aortic stiffness may contribute directly to renal injury by favoring increased transmission of PP to the renal microcirculation (Bidani & Griffin, 2004). Unlike benign and malignant nephrosclerosis, the histological lesions are glomerular, being characterized by glomerulosclerosis (Bidani & Griffin, 2004).

4.3 Clinical studies – Relation between SBP/PP and renal vascular nephropathy

Several longitudinal and cross-sectional studies indicate a relation between an increase in arterial stiffness and its corollaries, increased SBP/PP, and injury to the renal microcirculation.

4.3.1 Essential hypertension

4.3.1.1 Systolic blood pressure (SBP)

In the Systolic Hypertension in the Elderly Program (SHEP) conducted in subjects older than 65 years with ISH, SBP emerged as the best predictor of an increase in serum creatinine within a 5-year period (Young et al., 2002). Similarly in a cohort of 722 subjects with treated essential hypertension, the decrease in GFR, within a 7-year observation period, was preferentially associated with baseline SBP (Vupputuri et al., 2003).

4.3.1.2 Pulse pressure (PP)

Other clinical investigations revealed an association between PP and decline in renal function in older subjects. Fesler et al reported that in 132 never treated essential hypertension patients at baseline followed on treatment for 6.5 years, the yearly change in GFR was strongly and inversely correlated with PP independent of baseline GFR, age, MAP, body mass index, and microalbuminuria (Fesler et al., 2007). Gosse et al reported similar findings (Gosse et al., 2009). Measured either on clinic examination or by ambulatory BP monitoring in 375 patients with uncomplicated essential hypertension without proteinuria over a mean follow-up period of 14 years, initial baseline PP was an independent determinant of decline in renal function, pointing to the role of BP pulsatility as a glomerular biotrauma (Gosse et al., 2009).

4.3.2 Chronic Kidney Disease (CKD)

Aortic stiffening has been shown to predict loss of renal function also in CKD. Ford et al evaluated the relation between arterial stiffness and changes in renal function in 120 patients with CKD stage 3 and 4 enrolled in the prospective ACADEMIC (Arterial Compliance and Oxidant Stress as Predictors of Loss of Renal Function, Morbidity and Mortality in Chronic Kidney Disease (CKD) study) cohort (Ford et al., 2010). These investigators noted that, compared to those with lower PWV (12.3 m/sec), patients with higher PWV (13.9 m/s) experienced a greater progression of CKD, as determined by a greater decrease in the reciprocal of serum creatinine and greater than 25% decline in estimated glomerular filtration rate during 1 year follow-up (Ford et al., 2010).

Conversely, decreasing renal function may promote risk of accelerated rate of aortic stiffening. In 1290 untreated normotensive and hypertensive subjects with a serum

creatinine $< 130 \mu\text{mol/L}$ ($< 1.47 \text{ mg/dl}$), Mourad et al reported an inverse association between aortic PWV and creatinine clearance calculated by the Cockcroft-Gault formula (Mourad et al., 2001). However the aortic PWV was significantly enhanced only in subjects exhibiting a reduced creatinine clearance in the lower tertile of normal values particularly in younger than 55 years of age. Baseline serum creatinine was the only predictor of the changes in arterial function (Mourad et al., 2001).

Similar associations between reduction in GFR and an acceleration of PWV were reported in the CRIC study in which unadjusted analysis indicated that each $10\text{ml/min}/1.73\text{m}^2$ decrease in estimated GFR was associated cross-sectionally with a 0.5 m/s increase in aortic PWV (Townsend et al., 2010).

In patients with ESRD (stage V), increased aortic stiffening, as measured by PWV may be a contributor to further deterioration in renal structure and function. Several uremia related factors have been postulated to account for the disease of the large arterial system (Udani et al., 2011).

4.4 Aging

The aging process is often associated with reduced renal function (Mimran, 2006). In the Multiple Risk Factor Intervention Trial (MRFIT), a high risk of ESRD was reported in patients with isolated systolic hypertension (ISH) (Klag et al., 1996). In a cohort of 212 patients with ISH, an inverse relationship between PP and GFR and effective renal plasma flow (ERPF) was documented in subjects 60 years of age and older independent of age, MAP and known cardiovascular factors (Verhave et al., 2005). This inverse relationship, however, was observed in elderly subjects exhibiting the highest tertile of PP (Verhave et al., 2005).

4.5 Microalbuminuria and pulse pressure

Increased urinary albumin excretion (UAE) is a well recognized risk for cardiovascular morbidity and mortality and a predictor of renal involvement (Sarnak et al., 2003).

The pathophysiologic mechanisms causing increased UAE have not been fully elucidated. However a link between BP and UAE is well recognized. Although earlier studies emphasized an association between DBP/MAP and UAE, more recent studies report stronger relations between SBP/PP and UAE (Farasat et al., 2010). In a cross-sectional study that included 211 untreated controls, patients with essential hypertension or clinically stable cardiovascular disease, Pedrinelli et al found that PP was the best predictor of UAE, defined as $\text{UAE} \geq 15 \mu\text{g/min}$ (Pedrinelli et al., 2000). Similarly in a longitudinal study of 450 normotensive and untreated hypertensive subjects drawn from the Baltimore Study of Aging, only longitudinal levels of SBP and PP, pulsatile BP components, were independent predictors of UAE in men (Pedrinelli et al., 2000).

4.6 Renal transplantation and pulse pressure

Increased PP, a sign of arterial stiffness, is frequently recorded in renal transplant recipients (Fernandez-Fresnedo et al., 2005).

Several studies have demonstrated a relationship between PP and renal allograft function and survival. In a cohort of 493 renal transplant recipients with a median follow-up of 6.3

years, increased PP, recorded 3 months post-transplant emerged as an early and strong marker of poor allograft outcome (Bahous et al., 2006; Vetromile et al., 2009). Further, recent data suggest that immunosuppressive regimens which include Calcineurin inhibitors may also mediate both an increased risk of arterial stiffness and allograft dysfunction (Seckinger et al., 2008). Adequate BP control and immunosuppressive therapy free of Calcineurin inhibitors have been recommended to improve allograft outcome and prevent nephrotoxicity (Seckinger et al., 2008 & Vetromile et al., 2009).

5. Cardiovascular disease and pulse pressure

Epidemiologic surveys and clinical observations have established a strong association between indices of arterial stiffness (peripheral PP, central PP, aortic PWV, pressure wave amplification) and cardiovascular events in hypertensive and older subjects.

5.1 Structural and functional changes in the cardiovascular system

Arterial stiffness is associated with structural and functional changes in the central elastic arteries (aorta and proximal elastic branches). These vessels dilate and stiffen (Lakatta, 2003). The primary cause of the stiffening is marked disorganization of the normal elastic pattern, increased deposition of less extensible collagen fibers, fibrosis, inflammation, medial smooth muscle necrosis, calcification and diffusion of macromolecules into the arterial wall (Lakatta, 2003). The repetitive cycles of distension of the arterial wall which occur with each heart beat lead to fatigue, fraying and fracture of the elastic fibers and subsequent extensive impairment of the medical elastin fiber network (Lakatta, 2003).

With increasing stiffness of the central elastic arteries, pulse wave velocity is faster, leading to summation of reflected and incident pulse waves in systole, enhancing central SBP, reducing DBP and widening central PP (Benetos et al., 2010). The elevation in central SBP increases myocardial oxygen demand, enhances left ventricular load, generates a heightened LV systolic pressure to sustain a constant blood flow and impairs ventricular ejection. Moreover, the contemporary reduction in DBP, the latter being a determinant of coronary blood supply, compromises coronary perfusion, predisposes to subendocardial ischemia, myocardial infarction and arrhythmias (Mosley et al., 2007). Both an elevated SBP and wide PP promote hypertrophy of the left ventricle, with impaired left ventricular relaxation and diastolic heart failure (Mosley et al., 2007). Finally, PP, an index of oscillatory hemodynamic forces, is a significant modulator of formation and rupture of atherosclerotic plaques (Mosley et al., 2007).

Endothelial dysfunction and reduced bioavailability of nitric oxide, frequently associated with arterial stiffness, impair and limit the vasoactive and antiatherosclerotic properties of the vascular endothelium (Mosley et al., 2007).

A cross-talk has been recently documented between the central elastic arterial system and microcirculation of target organ damage (O'Rourke and Safar, 2005). Arterial stiffness and PP have a negative impact on the microcirculation of the kidney and brain, predisposing to renal impairment and deterioration in neurocognitive function (O'Rourke and Safar, 2005).

5.2 Clinical studies

Recent prospective and retrospective epidemiologic and clinical studies have demonstrated that an elevated PP is independently related, in both middle aged and older subjects, to an increased risk of cardiovascular events. In two independent French untreated male cohorts, the IPC (Investigations Preventives et Cliniques) composed of 15561 men aged 20 to 82 years who had 2 visits spaced 4 to 10 years apart, and the Paris Prospective Study including 6246 men aged 42 to 53 years examined over a period of 4 years, Benetos et al reported that an increase in SBP combined with a reduction in DBP, a hemodynamic pattern characteristic of wide PP, was associated with a highest risk of cardiovascular mortality, independent of age, initial BP levels and other risk factors (Benetos et al., 2000). In a different study, these same investigators noted that in untreated subjects, a spontaneous evolution towards a pattern of combined increase in SBP and reduced DBP over an extended period was associated with a 2 fold increase in cardiovascular mortality compared to those without changes in SBP and DBP (Benetos et al., 2000).

The relationship between pulsatile BP components and risk of cardiovascular events was also explored in 1109 patients with coronary artery disease. Intra-aortic BP indices were recorded during coronary angiography in these patients (Jankowski et al., 2008). After a 4.5 year follow-up, the ascertained primary endpoints (cardiovascular death, myocardial infarction, stroke, cardiac arrest, cardiac transplantation or myocardial revascularization) occurred in 22% of the patients (Jankowski et al., 2008). Central pulsatility (defined as PP/MAP) and central PP emerged as the primary endpoints with ratios of 1.3 and 1.25 respectively suggesting that central pulsatile BP indices were more important determinants of risk of cardiovascular events than steady BP components in patients with coronary artery disease (Chirinos et al. & Jankowski et al., 2008).

Premature stiffening of the arterial tree is frequently reported in insulin resistance and diabetes (Kengne et al., 2009 & Stehouwer et al., 2008). In the recent ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron- Modified Release Controlled Evaluation Study) a clinical trial which enrolled 1140 subjects with type 2 diabetes, older than 55 years and one additional cardiovascular risk factor, the hazard ratio for cardiovascular events was 1.17 for SBP, 1.20 for PP, 1.12 for MAP and 1.04 for DBP. The investigators concluded that SBP and PP were the two best and DBP the least effective determinants of risk of major cardiovascular outcomes in relatively older diabetic patients (Kengne et al., 2009).

PP has been shown to be a predictor of heart failure especially in the elderly. In a sample of 2512 subjects aged ≥ 65 years, participants in the Established Population for Epidemiologic Study for the Elderly Program free of cardiovascular heart disease (CHD) and congestive heart failure (CHF) at baseline, a 10mmHg increment in PP was associated with an increased risk of CHD, CHF and overall mortality of 12%, 14% and 6% respectively both in normotensive subjects and in those with ISH (Vaccarino et al., 2000).

6. Cerebrovascular disease, stroke, neurocognitive dysfunction and pulse pressure

Several studies, in both population and patient-based cohorts have demonstrated a strong association between increased brachial PP and excess risk of stroke and neurocognitive

dysfunction in both elderly and middle aged subjects (Hanon et al, 2005; Paultre & Mosca, 2005).

6.1 Mechanisms of cerebrovascular events

An increased arterial stiffness can enhance the risk of stroke through several mechanisms. An elevation in central PP enhances arterial remodeling both at the site of the extracranial and intracranial arteries, increasing carotid wall thickness, and predisposing to carotid stenosis, formation of atherosclerotic plaques and the likelihood of their rupture (Laurent et al., 2009). Central PP has been associated with increased prevalence and severity of cerebral white matter lesions (Kim et al., 2011 & Scuteri et al., 2011). A second mechanism relates to the specific features of the cerebral circulation. The torrential cerebral blood flow and low cerebrovascular resistance expose the cerebral microcirculation to high pressure fluctuations in the carotid and vertebral arteries which tend to increase three-to fourfold with age (O'Rourke & Safar, 2005). Finally, coronary heart disease and heart failure, often associated with arterial stiffness and high central PP, are also risk factors for stroke (Selvetella et al., 2003).

6.2 Clinical studies

Several epidemiologic surveys and clinical studies have documented that, in the elderly, high brachial PP was more predictive for stroke incidence and mortality than elevated SBP (>140mmHg). In the Boston Veterans Administration Study, PP was a stronger predictor for fatal cardiovascular outcome than were SBP and DBP among elderly subjects aged 60-85 years (Waldstein et al., 2008). Similar observations were reported in a prospective study of 5092 Chinese subjects. In this study, the incidence of total stroke, either ischemic or hemorrhagic, was related to PP (Zhang et al., 2004). In contrast, several other prospective studies identified SBP as a stronger predictor for incidence and mortality of stroke than PP (Miura et al., 2009).

Further, there is growing evidence that response of PP to antihypertensive therapy may also be relevant to outcome. In a post-hoc analysis of Systolic Hypertension in the Elderly Program (SHEP) trial data, an increase in PP (>10mmHg) on active drug treatment was associated with an increased risk of stroke (Vaccarino et al., 2001).. Another analysis of the same study revealed the enhanced risk of stroke resulted from excessive reduction in DBP with a threshold at about 60mmHg (Somes et al., 1999).

Elderly patients often have multiple comorbid conditions. These subjects are at increased postoperative complications when undergoing major surgical procedures. In a recent prospective study, a high brachial PP (>72mmHg) was reported to be associated with an increased risk of stroke during the postoperative period (Benjo et al., 2007).

In contrast to the well established relationship between brachial PP and risk of stroke in the elderly, data in middle aged subjects are controversial. A meta-analysis of prospective cohort studies reported that PP was not an independent risk factor for stroke. However, in a recent large cohort Japanese study which included 33372 participants free of cardiovascular disease at baseline and followed for 12 years, the JPHC study, PP was an independent stroke predictor among middle aged subjects with SBP<140mmHg, but not among those with higher SBP (Okada et al., 2011). Among persons of SBP<140mmHg, a 10mmHg higher PP at

baseline was associated with 8.31mmHg higher SBP and 1.69mmHg lower DBP at baseline (Okada et al., 2011). These data suggest that, in middle aged subjects with SBP<140mmHg, it is the low DBP rather than the non hypertensive SBP which impacts the excess stroke risk (Okada et al., 2011).

Increased brachial PP is also a risk predictor for neurocognitive dysfunction in healthy elderly and middle aged normotensive and hypertensive individuals (Robbins et al., 2005). Impairment of cognitive function and memory loss are frequent in the aging population, especially among the elderly subjects (Henskens et al., 2008). Alzheimer's disease and vascular dementia are the most devastating manifestations of these neurocognitive disorders. Several longitudinal studies have emphasized an association between these dementias with increased PWV and a wide brachial PP, both indices of increased arterial stiffness (Qiu et al., 2003). In a community based cohort of 1270 elderly subjects (mean age \geq 75 years) free of dementia at baseline, higher brachial PP (> 84 versus 70-84mmHg) was associated with increased risks of both Alzheimer's disease and vascular dementia (adjusted relative risks of 1.9 and 1.7 respectively) (Qiu et al., 2003). The association was particularly pronounced among women.

7. Therapeutic approaches

It is well established that reduction in BP and or improvement in arterial stiffness are associated with a reduction in risk of cardiovascular events (Dart & Kingwell, 2001). However it is often difficult to separate the effects of antihypertensive therapy on BP reduction alone from their direct effects on vascular wall properties. In fact, interventions that reduce BP and improve cardiovascular outcome are often associated with improvement in indices of arterial stiffness (PWV, PP) (Laurent et al., 2006; Laurent & Boutouyrie, 2007; Van Bortel et al., 2001).

Therapeutic mechanisms include both lifestyle issues and pharmacologic treatment.

7.1 Lifestyle measures

A large number of lifestyle measures have been postulated to reduce both BP and arterial stiffening. These include body weight reduction, exercise, lowering salt intake, smoking cessation and moderation of alcohol consumption.

7.1.1 Weight reduction

Intentional weight reduction in obese hypertensive subjects is associated with significant fall in BP. Several clinical studies have shown that obese subjects whether normotensive or hypertensive exhibit increased arterial stiffness with its associated hemodynamic indices (increased PWV and PP) (Orr et al., 2008). In these subjects, weight loss with a hypocaloric diet improved arterial stiffness and reduced PWV and PP (Dengo et al., 2010). In some studies, an improvement in endothelial function was also reported (Miyaki et al., 2009).

7.1.2 Dietary supplement

Several dietary supplements appear to improve functional characteristics of the elastic arterial system. Supplementation with n-3 polyunsaturated fatty acids reduces arterial

stiffness in dyslipidemic subjects, probably by decreasing serum triglycerides (Nestel et al., 2002). A high dietary intake of isoflavones, the non-steroidal plant derived compounds rich in soy beans, and administration of red clover isoflavones reduce PWV (Van Der Schouw et al., 2002). These effects have been attributed to the affinity of isoflavones to human estrogen receptors.

Recent reports have demonstrated that cocoa use ameliorated endothelial function, as evidenced by improved endothelial flow mediated vasorelaxation (Ferri, 2006). Changes were more striking in older subjects. The amelioration in endothelial function has been attributed to the flavanols, a subclass of flavanoids, present in large quantities in cocoa beans (Ferri, 2006). Controlled experiments conducted with beverages rich in flavanoids (wine, fruit, vegetable, tea, purple grape juice) have documented similar endothelial benefits (Ferri, 2006).

The cocoa related improved endothelial functions have been linked to increased bioavailability of nitric oxide (Ferri, 2006). In clinical trials, cocoa supplementation has been associated with BP reduction in subjects with grade I hypertension, with ISH and in younger soccer players (Ferri, 2006; Taubert et al., 2003).

7.1.3 Salt intake

Salt is the most potent modulator of arterial stiffness (Zieman et al., 2005). High salt intake enhances the age-related changes in the vascular system (Zieman et al., 2005). High salt intake increases MAP and triggers structural and functional pressure-independent changes in the vascular wall. In experimental animals, exposure to high salt diet has been associated with alterations in the composition of the vascular wall that precede BP elevations by several weeks (Limas et al., 1980). In the human, short- and long-term salt restriction causes an improvement in arterial distensibility independent from the effect on BP levels (Aviolo et al., 1986). In a group of elderly subjects (mean age 64 ± 2 years) with isolated systolic hypertension, dietary salt restriction for 4 weeks was associated with fall in both supine resting SBP (≈ 6 mmHg), ambulatory SBP (≈ 3 mmHg) and enhanced carotid artery compliance by 46% (Gates et al., 2004).

7.1.4 Alcohol consumption

An association between alcohol consumption and increased arterial stiffness has been reported in several studies (Sierksma et al., 2004; Zieman et al., 2005). Conversely, moderation of alcohol intake appears to reduce significantly PWV in both genders, independently of changes in BP levels (Sierksma et al., 2004; Zieman et al., 2005).

7.1.5 Physical exercise

The age related increase in arterial stiffness can be partly reversed by a program of physical training. In middle aged sedentary men, 3 months of aerobic training (walking or jogging 40 minutes daily at 70-75% of maximum heart rate) enhanced arterial compliance to levels observed in similarly aged endurance trained subjects (Tanaka et al., 2000). However, moderate exercise does not appear to improve arterial stiffening in elderly subjects with isolated systolic hypertension (Miyachi et al., 2003; Tanaka et al., 2000; Zieman et al., 2005).

In contrast, resistance training (weight lifting) has been reported to increase arterial stiffness and is associated with more severe increase in left ventricular mass compared to sedentary controls (Bertovic et al., 1999).

7.2 Pharmacologic approach

Although antihypertensive therapy has targeted brachial (peripheral) BP parameters, recent studies suggest that control of central hemodynamic indices (central SBP, PP, PWV) afford better cardiorenal protection (The CAFÉ Investigators, for the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Investigators, 2006).

The therapeutic benefits of antihypertensive drugs are influenced by two major effects: i) the effect due to BP reduction; ii) the direct effect of the drug on the vessel wall (Weber et al., 2005). Drug therapy that favorably influences blood vessel function appears to directly enhance the mechanical properties of arterial wall, independent of BP changes. In a therapeutic trial on patients with endstage renal failure, a population at very high cardiovascular risk, longer survival was strongly related to the drug-induced reversibility of aortic stiffness measured by PWV independently of BP evaluation (Guerin et al., 2001).

Although all classes of antihypertensive drugs reduce BP effectively, they do not exert similar benefits on arterial structure and function (Van Bortel et al., 2001). Antihypertensive therapy should focus on modulating high PP, the latter parameter contributing to major risk of cardiorenal events in older hypertensive subjects (Van Bortel et al., 2001). In these subjects who frequently exhibit ISH or a disproportionate increase in SBP over DBP, causing a selective widening in PP, the goal of treatment should aim at decreasing SBP with maintenance or even enhancing DBP. These targets may be attained by an active improvement in arterial stiffness, change in wave reflection and reduction in left ventricular ejection (Van Bortel et al., 2001).

Inhibitors of the renin-angiotensin-aldosterone system (RAAS), calcium channel antagonists, nitrovasodilators, diuretics and 3-methylglutaryl-coenzyme A inhibitors (statins) appear to modulate arterial stiffness (Staessen and Birkenhager, 2005).

The RAAS inhibitors reduce arterial stiffness by inhibition of the vasoconstrictive action of angiotensin II and improvement in endothelial function (Van Bortel et al., 2001). In a substudy of the RENAAL clinical trial, administration of Losartan to diabetic patients with baseline PP \geq 90mmHg led to 53.5% risk reduction for ESRD alone and 35.5% risk reduction for ESRD or death (Bakris et al., 2003). A similar mode of action has been postulated for the aldosterone antagonists (Van Bortel et al., 2001). Calcium channel blockers, by exerting direct relaxing effects on vascular smooth muscle cells, appear to also achieve a reduction in arterial stiffness and wave reflection. Nitrovasodilators effectively reduce central SBP and PP, especially in patients with stiff arteries and enhanced wave reflections. The benefits provided by nitrates and phosphodiesterase type-5 inhibitors have been attributed to the increase in cyclic guanosine monophosphate in vascular smooth muscles (Weber et al., 2005). Diuretics reduce arterial stiffness by decreasing systemic BP (Cushman et al., 2001 & Weber et al., 2005).

In contrast, in clinical trials, atenolol or pure beta-blockade based-therapy did not provide cardiovascular protection compared to that afforded by newer classes of BP lowering agent,

despite similar brachial BP levels (Conduit Artery Function Evaluation [CAFÉ] Study – Anglo Scandinavian Cardiac Outcomes Trial [ASCOT], 2006).

Administration of statins to overweight and obese subjects was associated with an improvement in arterial stiffness as evidenced by a significant reduction in PWV, independent of baseline cardiometabolic risk factors (Orr et al., 2009).

8. Conclusion

Increased PP, defined as the difference between inappropriately elevated SBP and reduced DBP at any value of MAP has recently emerged as an important and independent predictor of enhanced cardiovascular morbidity and mortality, especially in senior subjects. Central PP represents a surrogate measure of increased arterial stiffness of the central elastic arteries. However, brachial PP is a widely accepted marker of arterial stiffness in older subjects due to loss of amplification phenomenon and equalization with central PP.

In the general population, PP and age are positively correlated after the age of 50 years, whereas a negative correlation between these 2 parameters is found in adults younger than 50 years.

Interaction between left ventricular outflow and elastic properties of the central arteries creates incident forward propagating and reflected backward traveling pulse waves which summate either in diastole or systole. In young adults, due to high arterial distensibility, both pulse waves summate in diastole boosting central DBP, whereas in older subjects, due to increased arterial stiffness, summation occurs in late systole, generating a high SBP and loss of peripheral amplification.

Epidemiologic surveys and clinical studies have demonstrated, in the elderly, a close relationship between increased brachial PP and cardiovascular events, stroke, impairment in neurocognitive function and dementia, and vascular nephropathy and progression of CKD.

Therapeutic regimens include lifestyle modifications and pharmacologic medications. Therapeutic benefits have been reported when BP reduction has been associated with improved arterial function and reduced arterial stiffness.

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Cardiovascular risk factors contribute to the development of cardiovascular disease from early life. It is thus crucial to implement preventive strategies addressing the burden of cardiovascular disease as early as possible. A multidisciplinary approach to the risk estimation and prevention of vascular events should be adopted at each level of health care, starting from the setting of perinatology. Recent decades have been marked with major advances in this field, with the emergence of a variety of new inflammatory and immune-mediated markers of heightened cardiovascular risk in particular. The current book reflects some of the emerging concepts in cardiovascular pathophysiology and the shifting paradigm of cardiovascular risk estimation. It comprehensively covers primary and secondary preventive measures targeted at different age and gender groups. Attention is paid to inflammatory and metabolic markers of vascular damage and to the assessment of vascular function by noninvasive standardized ultrasound techniques. This is a must-read book for all health professionals and researchers tackling the issue of cardiovascular burden at individual and community level. It can also serve as a didactic source for postgraduate medical students.

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