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Review Article

AN ELEVATED PULSE PRESSURE: A MAJOR RISK FACTOR FOR CARDIOVASCULAR DISEASES

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ABSTRACT

Pulse pressure (PP) is a predictor and major risk factor for cardiovascular (CV) diseases as left ventricular hypertrophy, myocardial infarction, carotid hypertrophy, atherosclerosis, congestive heart failure and stroke as well as chronic renal failure progression. PP has been proved a strong forecaster of CV risk, particularly when it is higher than 60 mm Hg and more strongly relates to carotid hypertrophy and extent of atherosclerosis than systolic pressure. Isolated systolic hypertension (ISH) is common among the elderly and is accompanied by elevated pulse pressure. However, treatment of ISH may further raise the PP if diastolic pressure is lowered to a greater extent than systolic pressure. Several drugs for hypertension have the side effect of increasing resting PP irreversibly, other antihypertensive drugs, such as ACE inhibitors, have been shown to lower the PP. Various approaches made by researchers for the maintenance of normal PP to reduce the mortality caused due to CV events based on the abnormal PP. We briefly review the therapeutic consequences for the attenuation of elevated PP associated with various CV events.

Keywords: Pulse pressure, Cardiovascular diseases, Arterial stiffness, Antihypertensive therapy.

INTRODUCTION

Pulse pressure is the pressure difference between systolic and diastolic pressures to create the pulse [1]. If resting blood pressure is (systolic/diastolic) 120/80mmHg, PP is 40 [2,3]. The systemic PP directly proportional to stroke volume (SV) i.e. the volume of blood ejected from the left ventricle during systole and inversely proportional to the compliance (C) of the aorta [4]. It can also be defined as the difference between the peak and the foot of the pressure wave, and it is indirect measure of pulsatile load on the left ventricle [5].

The SV and C can be used to calculate the pulse pressure:

$$PP = SV / C$$

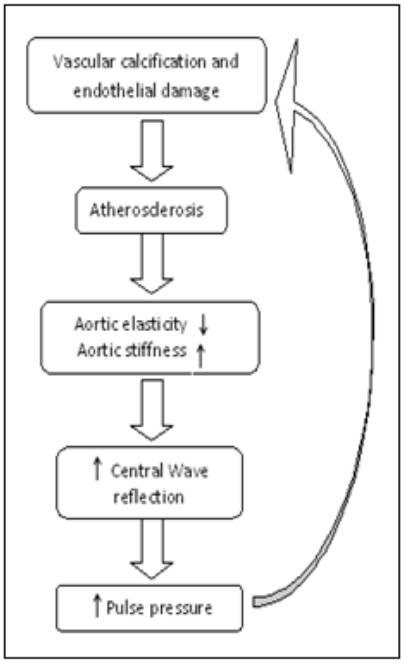
PP is determined by both cardiac and vascular factors. The cardiac ventricular ejection generates a primary pressure wave and heart rate has an independent influence on the shape of this wave [6]. Both longitudinal and cross-sectional components of the vascular system contribute to the shape of the arterial pressure wave and, thereby, to pulse pressure. The longitudinal constituent is the structural design of the arterial tree, which determines the major reflection sites for the pressure wave. The cross-sectional design of the vascular system consists of a geometric (diameter) and a structural (composition of vessel wall) component. Both diameter and composition of the vessel wall vary greatly when going from central to more peripheral arteries [7,8].

Low (narrow) pulse pressure

A pulse pressure lesser than 40 indicates patient have poor heart function, while a higher PP may mean heart's valves are leaky (valve regurgitation). A number of factors are known to influence arterial wall behavior and therefore, PP [9]. It is considered abnormally low if it is less than 25% of the systolic value. In trauma a narrow PP suggests significant blood loss (insufficient preload leading to reduced cardiac output). If it is extremely low, i.e. 25 mmHg or less, the cause may be low SV, as in congestive heart failure and shock [10,11].

Elevated pulse pressure

Elevated PP can result from either elevated systolic blood pressure (SBP) or low diastolic blood pressure (DBP) or both [12]. The DBP peaks at and subsequently declines after age 55 years, while the SBP augments relentlessly with each decade of life [13,14]. Other causes of a widened PP, including severe anemia, aortic insufficiency, thyrotoxicosis or arteriovenous shunting, are much more uncommon [15]. An individual might have an elevated PP, but may or may not be hypertensive (e.g., BP = 190/130, PP = 60 mmHg, vs. BP = 125/65, PP = 60 mmHg). Similarly, an individual might have an elevated SBP, but may or may not have a widened PP (e.g., BP = 150/90, PP = 60 mmHg, vs. BP = 150/110, PP = 40 mmHg) [1,16]. If the usual resting PP is consistently greater than 40 mmHg, e.g. 60 or 80 mmHg, the most likely basis is stiffness of major arteries, atherosclerosis and vascular calcification, aortic regurgitation, arteriovenous malformation, hyperthyroidism or some combination [17,18].



Pulse pressure is a function of SBP and DBP and is dependent on SV and arterial wall elastic properties [19,20]. In a young healthy person, each SV received into the central vessels is accommodated by a stretching of these vessels in systole followed by subsequent elastic recoil in late systole and diastole. This is known as arterial C and has the effect of maintaining central and peripheral BP within a relatively narrow range. With aging, there is a disruption and

fragmentation of the elastic lamellae of the central arteries, as well as alteration of the collagen-to-elastin ratio [21], leading to arterial stiffness, loss of C, and increased PWV and therefore increased PP [22,23]. In hypertension to older age, arterial stiffness increases, diastolic decreases, central systolic and pulse pressures are augmented due to increase in pulse wave and early revisit of waves from the periphery to the heart [24]. Bidirectionality property of elevated PP mentioned in figure 1.

Clinical events related to elevated PP

Epidemiological studies in the past decade have stressed the importance of PP as an independent prognostic marker for cardiovascular morbidity and mortality [7,25-29]. Panagiotakos and colleagues, in a seven-country prospective study of 12,763 people living in the United States, Japan, Italy, Greece, Finland, former Yugoslavia and The Netherlands, identified PP, followed by DBP and SBP, as the best predictor for CVD mortality over the twenty-five-year follow up period [1,30].

Hypertension with elevated PP causes more arterial damage compared to high BP with normal PP [17]. Hypertensive patients of older age with higher PP and associated with diabetes, generally prefers calcium channel blockers and diuretics for treatment. The higher PP is sometime associated with elevated LV mass [31] and cause LVH, prolonged isovolumic relaxation time and higher stroke index. Elevated PP may associate with both increased SV and arterial stiffness [13,32]. A number of studies in humans and rats suggest consistent associations between body weight and arterial stiffness, independent of age, MAP and HR [33].

Various factors such as reduction of elastic fibres in arteries [21], an increased expression of substances (endothelin, thromboxan, etc.) for their vasoconstriction properties and decrease in substances (bradykinin, nitric oxide) that produces vasodilation are responsible to elevate the pulse pressure [26].

Cardiovascular diseases associated with elevated pulse pressure

With aging, the cardiac load tends to increase, because of a disproportional augmentation of central than brachial arterial stiffness that raises central PP and thus reduces peripheral PP augmentation [15,34]. This process favors the development of cardiac hypertrophy and/or CHF [35-38]. High PP is predictor of cardiovascular death after myocardial infarction as well as chronic renal failure progression [39-42]. If the PP is low usually, it reflects a low SV and this means that heart is not pumping out the right amount of blood that it is supposed to. This could be due to a very serious problem like CHD or shock [10]. A low PP ≤20 mmHg, in a blood pressure of 90/70 mmHg for example, may represent a decrease in cardiac output [43] and reflects a reduction of SV due to left ventricular dysfunction [10,14].

Arterial stiffness, the hallmark of vascular aging, magnifies the augment in BP during systole and its decline during diastole [44]. Pulse pressure is an established index of arterial stiffness. It reflects the age-related deterioration of the elastic properties of the large arteries. Decreased arterial elasticity independently predicts the risk of cardiovascular events [29,45-47]. Arterial stiffness is a general term that collectively describes distensiblity, C, and elastic modulus of the arterial vascular system. It can be measured by using a simple technique i.e. pulse wave analysis (PWA) [48] which is noninvasive technique and used in epidemiological [49] and interventional studies [50]. It gives information about mechanical properties of the arterial structure [51] and can also be used to evaluate function of endothelial cells [52].

Increase in arterial stiffness and premature vascular aging are coupled with decreased glomerular filtration rate and is indicator of chronic renal disease progression and end-stage renal disease (ESRD) [53]. In a study, it was found that increased arterial stiffness is associated with smaller PP amplification with increasing adiposity and hence obesity/overweight is associated with higher systolic pressure and PP [54]. Untreated hypertension accelerates the rate of development of large artery stiffness and perpetuates a vicious cycle of accelerated hypertension, further increasing the arterial stiffness and hence PP. Appropriate control of BP could reduce the hypertension-induced progression of arterial stiffness [55]. Elevated PP is associated with an increased risk of CV death in patients on peritoneal dialysis (PD). Recognition of this characteristic as an important predictor of mortality suggests that one goal of antihypertensive therapy in PD patients should be to decrease elevated pulse pressure [56]. Elevated pulse pressure are responsible for the stretching of arteries, provoke weariness and rupture of elastic elements, and rupture of aneurysms that leads to atherosclerosis and thrombotic events [34].

Elevated PP is also associated with cognitive decline and increased risk of Alzheimer's disease (AD) in older adults. Sixty-five elderly patients (mean age 74.2 years) clinically diagnosed with possible or probable AD underwent neuropsychological testing and BP examinations. Results demonstrated that antemortem PP elevation was associated cerebrovascular disease at autopsy suggests that in older adults with AD, PP elevation may increase the risk of cerebrovascular disease. These findings may have treatment implications since some antihypertensive medications specifically address the pulsatile component of BP (e.g., renin-angiotensin system (RAS) inhibitors and CCB) [57].

SBP and PP appear to be the major determinants of the tone of the afferent arterioles, independent of MAP and DBP [58,59]. In fact, recent clinical studies indicate that hypertensive renal injury correlates most strongly with SBP and PP [60,61]. Excess PP has also been recognized to cause vascular injury in the systemic circulation predicting adverse cardiovascular outcomes, unaffected by current antihypertensive therapy [62]. A PP combined with bradycardia is associated with increased intracranial pressure. A high resting PP is unsafe and tends to speed up the normal aging of body organs, particularly the heart, the brain and kidney.

Approaches for Treatment

A number of studies have been carried out to compare the effects of different agents and classes on arterial properties that are relevant to the issue of PP. Several studies have identified that high PP is affected differently by different hypertensive agents [17], despite similar effects on peripheral (brachial) BP [63]. Lifestyle and dietary modifications like smoking cessation [64], use of unsaturated fatty acids [65], isoflavones [66], less intake of dietary salt [67], regular exercise [68], and limited alcohol consumption [69,70] may helps to maintain the normal vascular stiffness. Pharmacologic interventions like use of antihypertensives as CCBs, diuretics, ACEIs, β-blockers, nitrates, phosphodiesterase-5-inhibitors, and statins to reduce the pulse pressure and hence arterial stiffness. Even though all these therapies lower blood pressure, their effect on arterial stiffness is only modest [15]. Optimal antihypertensive drug should decrease SBP and arterial stiffness without an increase of pulse pressure.

Angiotensin converting enzyme inhibitor (ACEI):

In a placebo controlled crossover study of acute effects of the ACEI, quinapril, in patients with essential hypertension, there were increase in carotid artery distensibility and aortic C (determined by PWV). The effects on aortic distensibility appeared to be a combination of direct and BP dependent effect [71]. Pulse pressure was reduced by similar amount at both carotid and brachial sites. In another study, intravenous dihydralazine or perindoprilat, did not alter significantly to the carotid-femoral PWV in patients with hypertension [72].

Twenty-seven hypertensive patients were randomised to receive lisinopril (20 mg) or losartan (50 mg) for 5 weeks, and were subsequently crossed-over to the alternative treatment for a second 5-week period. Lisinopril was found more effective than losartan in reducing elevated pulse pressure [73]. Antihypertensive agents acting as vasodilators, such as ACEIs and ARBs, have been shown to improve arterial C [73,74,75]. In an animal study, pulse pressure was reduced in the captopril-treated spontaneously hypertensive rats (SHR) [76].

In a study on 24 normotensive elderly subjects, administration of an ACEI ameliorated age-related increase in carotid arterial stiffness [77]. In the regression of arterial stiffness in a Controlled Double

Blind Study trial, the ACEI perindopril decreased aortic systolic and pulse pressure superior than the β-blocker atenolol [78]. In another study, all class of antihypertensive drugs decreased MAP in spontaneous hypertensive rats, only the CCB, nicardipine and ACEI, perindoprilat reduced proximal pulse pressure. This dissociation between the effects on MAP and proximal and distal PP can be explained by the preferential action of the different antihypertensive agents on large arteries and wave reflections, producing different patterns in the pulsatile component of the heart load [79]. In older men, ACEIs alone or in combination with diuretics may be more effective in lowering mean PP [80].

In an open randomized cross-over trial on sixty seven chronic kidney diseased (CKD) patients, combined RAS blockade with enalapril and candesartan caused additive significant BP independent reduction in aortic PWV and arterial stiffness compared to monotherapy [81]. However in another study, omapatrilat, a combination ACEIs and vasopeptidase inhibitor reduced arterial stiffness and consequently PP better than the ACEI, enalapril [40]. Ramipril produced BP independent reduction in aortic PWV in hypertensive subjects treated for 6 weeks [82].

In a retrospective analysis of the hypertensive subjects of the multicenter double-blind study, in which fixed first-line antihypertensive combination therapy with an ACEI, perindopril (2 mg), and a diuretic, indapamide (0.625 mg), found more effective than atenolol in normalizing PP [83]. Antihypertensive therapy with angiotensin II receptor blockers (losartan) or ACEI (trandolapril) has been shown to have a beneficial effect on atherosclerosis or arterial stiffness in patients with ESRD [84,85].

In this study, 101 patients with mild essential hypertension were randomly assigned to an 8-week period of monotherapy with enalapril 10 mg a day or indapamide 2.5 mg a day. Central as well as brachial systolic, augmented, and pulse pressure were determined. Results infer a reduction in wave reflection with enalapril, causing a fall in aortic pressure augmentation, and a corresponding reduction in aortic systolic and pulse pressure. Results showed that a diuretic, a β-blocker agent, is not as effective a therapy as an ACE inhibitor in reducing pulse pressure [86].

Angiotensin receptor blockers

In a seven randomized, double blind, placebo controlled studies, 6 to 12 week efficacy trials of olmesartan 20 mg and 40 mg/day were analyzed to determine changes in SBP and PP. Olmesartan significantly reduced SBP and PP, and these reductions were more pronounced in patients with a wide baseline PP [87]. In a 4 week single blind randomized crossover study, effect of losartan (50 mg/day) to hydrochlorthiazide (12.5 mg/day) on BP and arterial stiffness was compared in 11 untreated hypertensive patients aged 47 to 69 years. Both drugs produced decrease in brachial BP but only losartan induced a decrease in arterial wave reflection with a preferential reduction in aortic compared to brachial PP. Losartan also increased PP amplification and reduced PWV. These results suggest that an AT1 receptor antagonist induces a BP independent decrease in aortic stiffness and arterial wave reflection [88].

Alpha- adrenergic blockers

In an acute invasive study in which aortic PWV was inferred from the first minimum of the impedence modulus, PWV was unaffected by beta adrenoceptor blockade but was reduced by combined alpha and beta blockade [89]. Alpha-adrenoceptor blocker not showed direct effect in the augmentation of PP in any study.

β-adrenergic blockers

When the antihypertensive effects of β-blockers were compared with those of thiazide diuretics, the researchers identified the difference in effect on DBP, indicating that β-blockers have little or no effect on PP, whereas, thiazides cause a significant dose-related decrease in PP [90,91]. In a study, the effect of carvedilol and its combination with captopril on PP, LVH, kidney vascular changes and kidney function in SHR with adriamycin nephropathy. Indicated that, carvedilol alone, but more sturdily in combination with captopril, reduced blood pressure, PP, LVH, renal blood vessel changes and chronic renal failure progression.[39] In another study, nebivolol and nitrates produced a significant lowering of pulse pressure and an increase of the arterial C suggesting a beneficial effect that could promote the regression of left ventricular hypertrophy [92].

In a retrospective study, compared three groups of hypertensive patients (aged 35-65 years) chronically treated with either ARBs, carvedilol/nebivolol or atenolol, matched for age (mean 52 years), sex (61% female), brachial BP and concomitant use of diuretics (75-81%) and dihydropyridine calcium antagonists (27-33%). Result indicated that, for similar brachial BP and aortic stiffness, treatment with either vasodilating β-blockers or ARBs associated with lower central systolic BP and wave reflections than treatment with atenolol, suggesting that the vasodilating β-blockers might exert more favourable central haemodynamic effects, compared with atenolol, which were more alike, although not completely equal, to those of the ARBs [93].

In a clinical trial, atenolol and losartan reduced brachial systolic and pulse pressure in the same amount. However, atenolol reduced aortic systolic and pulse pressure 28 and 11 mm Hg, respectively, whereas losartan reduced aortic systolic and pulse pressure 40 and 23 mm Hg, respectively. Atenolol had little effect on radial and aortic augmentation indices, whereas losartan had a marked lowering effect [94,95].

Calcium channel blockers (CCBs)

In the Anglo-Scandiavian Cardiac Outcomes Trial (ASCOT), CCB reduced risk of stroke about 27 %. In the same study, statin therapy did not lead to a reduction of central BP or augmentation index [96]. In a double blind, crossover comparison of 12 weeks treatments with the felodipine (a CCB) or the diuretic hydrochlorthiazide in subjects with mild to moderate hypertension, there were more pronounced fall in PWV at carotid-femoral as well as peripheral sites with felodipine. The finding of brachial artery dilation with felodipine, but not hydrochlorthiazide, however, indicated direct arterial wall effects of the CCB [97]. In a study of 8 months treatment to hypertensive subjects, nicardipine improved the peripheral C, determined by brachial radial PWV measurement but not by the atenolol [98]. The lowest central aortic pressures were achieved with calcium-blocking drugs and diuretics [99].

In a study spontaneous hypertensive rats chronically treated with verapamil, MAP was unchanged and PP was reduced, whereas carotid internal diameter, medial thickness and collagen content were reduced to some extent in normotensive rats [100]. The dose of verapamil principally lowered basal pulsatile vascular load and ventricular systolic contractile function, reflecting reductions of systolic ventricular and vascular stiffening [101].

Diuretics and vasodilators

In a cross-sectional study on 1429 subjects aged 60 years or older who reported receiving one or two hypertensive drugs from the following medication classes: β-blockers, diuretics, CCBs, or ACE inhibitors. Older hypertensive subjects who used diuretics alone or in combination with β-blockers had lower mean pulse pressure as compared with those using other agents or β-blockers alone. These findings lend support to recommendations for use of diuretics in older hypertensive patients [17,102]. One more study on hydrochlorothiazide and clonidine, produced reductions in PP, but clonidine was associated with a much higher incidence of side effects and drug withdrawals, and central α-agonists have not been shown to reduce cardiovascular events as initial therapy in clinical trials [103]. In a comparative study of five antihypertensive agents of some classes: two ACEI i.e. perindopril and captopril, isradipine (CCB), hydralazine (a vasodilator) and metoprolol (β-blocker) indicated that a reduction in PP and HR during antihypertensive treatment might be important in preventing the development of abnormal small artery structure in hypertension [32].

In a 10-year study on 640 hypertensive subjects at the outpatient department of the Abidjan Heart Institute, the keypoint was to find out the prevalence of a high PP, the correlation between PP and CV risk factors, the impact of PP on target organs, and the variation in PP while on treatment during follow up. Dual therapy with a diuretic

was reported to have greater effect in controlling the pulse pressure compared to patients without a dual diuretic [104].

Nitrates

Nitrates (e.g. isosorbide mononitrate, nitroglycerin) decrease PP higher than MAP and are prescribed for the treatment of isolated systolic hypertension (ISH). Nitrates produce drug tolerance during chronic treatment so an asymmetric dosing regimen may prevent loss of effect of nitrates [25,105,106]. Nitrates not influence aortic stiffness even though they reduced PP by selective endothelium-independent vasorelaxation and attenuation of peripheral wave reflection [15,107,108]. Nitroglycerin lowers mean BP in both age groups but reduces PP only in the old age group [109]. In a longitudinal cohort design study, PP, pulse wave and augmentation pressure were estimated in 411 female twins over a mean follow-up of 10.8 years. In a subsample (n=42), PP, arterial stiffness and arterial diameters were measured before and after nitroglycerin administration (400 µg s/l). It was observed that age-related widening of central PP is driven in large part by an increase in AP, which can be reversed by selective dilation of muscular arteries, independent of PWV [25].

Other

A study reported that 5 mg of folate daily over a three-week period reduced PP by 4.7 mmHg compared with a placebo and concluded that folic acid is an effective supplement that targets large artery stiffness and may prevent ISH [110]. Phosphodiesterase-5 inhibitors like sildenafil work similarly to nitrates and also reduce wave reflection and lower PP, but without the side effects of nitrates [111].

Conclusion

Pulse pressure is a biomarker of a number of cardiovascular diseases and the risks increases when it is higher than 60 mmHg. Pulse pressure is directly proportional to the arterial stiffness and incessantly increases with aging and hence increasing the risk of cardiovascular events. Various approaches have been made by the researchers for the attenuation of elevated pulse pressure to reduce mortality causes due to CVD associated with it. Antihypertensive drugs such as ACE inhibitors and ARBs reduced the elevated pulse pressure greater than the other class of antihypertensives. A diuretic in combination with β-blocker reduces PP effectively as compared to monotherapy. α-blockers are not effective in the augmentation of PP, whereas, verapamil (CCB) reduces systolic pressure and vascular stiffening. Nitrates decreases PP more than MAP but develops tolerance during chronic treatment. Monotherapy with hypertensive drugs is not sufficient to reduce widened pulse pressure effectively, hence, there is need of combination or supplementation with another drug or supplement diet (containing folic acid or Vitamin E) that helps to reduce the arterial stiffness. However, there is necessitate of more research in the field of therapies that specifically target PP, rather than mean pressure to control the CVD caused due to widened pulse pressure.

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