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Pulse Pressure

An Important Tool in Cardiovascular Pharmacology and Therapeutics

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Abstract

Epidemiological studies in the past decade have stressed the importance of pulse pressure (PP) as an independent risk factor for cardiovascular morbidity and mortality. We briefly review the epidemiological evidence and discuss the pathophysiological mechanisms which involve arterial stiffness and wave reflections in older patients. We discuss the therapeutic consequences of targeting PP rather than systolic (S) or diastolic (D) blood pressure (BP) when using antihypertensive agents. With this line of evidence it is important, first, to determine what minimal PP level indicates cardiovascular risk and, second, to note that an increasing number of clinical studies indicate that PP is poorly sensitive to placebo, while SBP and DBP are conversely highly sensitive. Finally, on the basis of large-scale intervention trials, PP seems to be an appropriate tool for studies of clinical pharmacology and therapeutics in the fields of hypertension, congestive heart failure and other cardiovascular diseases.

There is accumulating data to support the contention that pulse pressure (PP) may be, in individuals over 59 years of age, a significant marker of cardiovascular morbidity, independently of mean blood pressure (MBP). A wide clinic PP (>63mm Hg) in individuals over this age was shown to be a marker of increased arterial stiffness,[1,2] and other studies have suggested its close association with carotid intima-media thickness and left ventricular mass.[3,4] Clinic brachial PP may also be an independent predictor of myocardial infarction or congestive heart failure in hypertensive and normotensive individuals as well as in patients with diabetes mellitus, chronic renal failure or with severe atherosclerosis.[5] PP appears also to be a more accurate predictor of cardiovascular mortality than either systolic blood pressure (SBP) or MBP alone in some populations.[5]

To date, PP has been mainly considered as an epidemiological tool, and has not been specifically studied as an important marker for therapeutic trials and drug treatment. The purpose of this review is to show that PP may be a useful determination for therapeutic trials and clinical management of cardiovascular diseases.

1. Systolic Blood Pressure and Pulse Pressure (PP) as Markers of Cardiovascular Risk

In recent years, epidemiological studies have clearly shown that, in individuals over 59 years of age, PP was an independent marker of cardiovascular risk and for myocardial infarction, but not for stroke.[6] PP plays a role in cardiovascular morbidity and mortality independently of MBP, as shown from statistical evaluations as principal component analysis.[6] Nevertheless, it is more difficult to demonstrate that, in older individuals (>59 years of age), PP may be a stronger marker of cardiovascular risk than SBP alone.

From a methodological viewpoint, the concept that PP may differ from SBP in terms of risk factor is difficult to demonstrate. PP is only the mathematical difference between SBP and diastolic blood pressure (DBP), and the problem of interpreting artefacts is raised, particularly because SBP and PP are highly correlated. However, in several studies in older individuals, it has been shown that the best predictor function of all possible linear combinations of SBP (positive correlation) and DBP (negative correlation) was similar to that of PP, indicating that their association was causal and not merely a statistical artefact.[6-8] However, there are some studies indicating that SBP and PP may be equivalent markers of cardiovascular risk, particularly in the older populations.[9-11] Indeed the interactions between age and high BP may explain some discrepancies in these older selected populations.[10,11] Whereas SBP increases constantly and continuously with age, DBP increases only until 50–60 years and thereafter remains constant and even tends to decrease. The curvature corresponding to the DBP decrement varies widely from one to another studied population, so that, in some examples, SBP may be considered as a marker of risk equal to or even higher than PP.[10,11]

In a large population of individuals >65 years of age, Blacher et al.[12] have shown that cardiovascular risk is related not only to an increase of SBP but also to a decrease of DBP. As shown in figure 1, cardiovascular risk increases markedly with age. However, at any given value of SBP, cardiovascular risk is higher when DBP is lower. This important finding has been confirmed by two independent longitudinal studies indicating that, during a 20-year follow-up, individuals with higher cardiovascular mortality rates were those who developed in parallel an increase in SBP and a decrease in DBP, in the absence of any antihypertensive drug treatment.[13] Furthermore, it was shown that in individuals >60–65 years of age, neither SBP nor DBP were superior to PP in predicting coronary risk.[7] It is noteworthy that, at these ages, increased SBP and PP cannot be due to an increased ventricular ejection and, thus, suggest a role for the same haemodynamic influences: increased aortic stiffness and altered wave reflections.[1] In the recent years, both of these factors

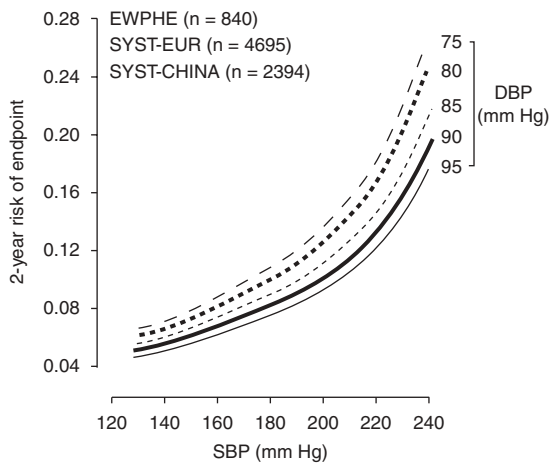

Fig. 1. Relationship between adjusted CV risk (y axis) and SBP (x axis) in a large European and Chinese population studied at baseline and issued from three therapeutic trials in participants ≥65 years of age.[11] CV risk increases with SBP level but, at any given value of SBP, CV risk increases when DBP is lower.[11] **CV** = cardiovascular; **DBP** = diastolic blood pressure; **EWPHE** = European Working Party on Hypertension in the Elderly trial; **SBP** = systolic blood pressure; **SYST-CHINA** = Systolic Hypertension in China study; **SYST-EUR** = Systolic Hypertension in Europe study.

have been shown to be independent markers of cardiovascular risk and to be even stronger predictors than SBP and/or PP.[14-16]

Finally, although PP is determined by combined haemodynamic cardiac (ventricular ejection) and arterial (arterial stiffness; wave reflections) factors, the individual PP is also influenced by other patient-related factors, which are either modifiable or non-modifiable (table I). Taking into account these conditions, it may be that PP is an appropriate tool to investigate cardiovascular pharmacology and therapeutics.

2. What PP Level Indicates Cardiovascular Risk?

Within the Gaussian distribution of BP, normal blood pressure is universally defined as SBP <140mm Hg and DBP <90mm Hg. From this arbitrary definition, two different populations, normotensive and hypertensive, may be defined from relatively simple calculations. Within this framework, the definition of normal values of PP is very complex. PP is the difference between SBP and DBP, and increased values may be observed both in the normotensive and the hypertensive population. For instance, an individual with a SBP/DBP value of 140/70mm Hg has the same PP as a hypertensive individual with a value of 170/100mm Hg. Thus, to evaluate PP, it is important both to establish references values and to determine their epidemiological assessment.

Asmar et al.[17] studied the reference values of brachial clinic PP, according to age and gender in a non-selected population of 61 724 individuals who were undergoing a routine systematic health examination (table II). After evaluation of mean values according to age and gender, a value of 50mm Hg was found to be the reference for clinical PP in both men and women. Adding two standard deviations gives 65mm Hg for clinic PP at risk. However, this value refers to casual measurements and values for ambulatory BP measurements remain to be established.[18]

Table I. Patient-related factors associated with pulse pressure

Modifiable factors	Non-modifiable factors
Mean blood pressure	Age
Cardiac structure and function	Gender
	Body height
	Diabetes and other cardiovascular risk factors

Table II. Reference values for clinic pulse pressure (PP) in a non-selected population. According to the mean values, a PP of 50mm Hg is likely the reference value in both men and women[17]

Population	No. of participants	Clinic PP (mm Hg)			
		mean	SD	50th P	95th P
Men	29 692	52	10	50	70
Women	31 416	49	10	50	65

P = percentile.

The point to emphasise here is that the 65mm Hg value concords with the 95th percentile of the distribution of the PP, and mostly is in close agreement with the clinic PP values reported to be associated with increased cardiovascular morbidity and mortality.[19-22] In the study by Gerdts et al.,[22] the group of patients remaining with a PP >63mm Hg was older, shorter, included more women and individuals with proteinuria and diabetes than individuals with a PP ≤63mm Hg. This group of patients was also characterised by less reduction in BP during 2 years follow-up. Finally, it is suggested that the 65mm Hg PP value should be considered as the threshold at risk both in the normotensive and the hypertensive populations, at least in men. Because cardiovascular risk is substantially different in men and women,[20,21] the specific role of gender needs to be better estimated in future trials.

3. Is There a Placebo Reactivity of PP?

One of the main characteristics of hypertension is the significant placebo reactivity of SBP and DBP, which is close to 15%.[23] The placebo response is more pronounced in older than younger individuals

and placebo responders need to be excluded from therapeutic trials. The study of the antihypertensive effect of a new antihypertensive agent constantly requires the use of placebo as the comparator. In the past, it has been proposed that ambulatory BP would have no placebo effect and that the placebo response occurred only with clinic blood pressure.[24,25] However, it is now admitted that only the difference of methodology is responsible for a less accentuated placebo effect with ambulatory BP measurements than with clinic BP measurements.[24,25]

A recent study was designed to evaluate the placebo effect on BP and to differentiate it from regression to the mean.[26] According to a crossover design, 26 patients with mild-to-moderate hypertension received placebo or no treatment, and were followed for 1 month. Clinic and ambulatory BP were assessed at baseline and at the end of each 1-month treatment period. Placebo administration resulted in significant reduction in clinic SBP, DBP and MBP ($p < 0.01$), ambulatory 24-hour SBP ($p < 0.05$), and daytime SBP, DBP and MBP ($p < 0.01$, $p < 0.05$, $p < 0.01$, respectively). No significant differences were noted for PP and heart rate, or between BP values measured at baseline and after 1 month without treatment. This study conclusively showed the effect of placebo in mild-to-moderate hypertension on both clinic and ambulatory SBP, DBP and MBP, in which it has been shown to differ from the regression to the mean phenomenon. Nevertheless, this effect was not observed for heart rate or PP. This finding has been further confirmed,[27,28] particularly using ambulatory PP measurements.[29]

4. PP and Therapeutic Trials: Prospective Views

In this review, we have shown that PP, a very simple calculated parameter, may be an appropriate tool in clinical cardiovascular pharmacology and therapeutics. Recent investigations have emphasised that PP may be used in therapeutic trials. A study of feasibility has been performed, showing that PP, in addition to pulse wave velocity (PWV), may be used as a specific endpoint in large-scale intervention trials.[30] Investigators from 80 centres (22 countries) participated in specific training sessions organised for small groups (46 persons) of investigators by a Training and Certification Committee. The criteria established for this quality control were the baseline stability of the recorded PWV and PP, the variations of the baseline according to pulse wave amplitude, the wave shape and the abrupt systolic upstroke of the initial parts of the pressure waves. This study took into account several important methodological aspects: (i) the certification procedures allowed the construction of an homogeneous database; (ii) online assistance and quality control limited the loss of data; and (iii) the electronic management of data directly acquired from computerised recordings had the advantage of saving data input time and preventing typing/input errors. These procedures, which may seem cumbersome and restrictive when setting up multicentre studies, have substantial benefits when one considers the low rate (under 10%) of data excluded for insufficient quality.

From all these methodological prerequisites, several findings have been reported to be useful in clinical pharmacology. First, a given antihypertensive agent may act dose-dependently on DBP without a parallel and a proportional decrease of SBP and PP.[31] Second, a comparison between two antihypertensive agents from the same class showed unequal effect on PP with different dose-effect relationships on SBP, DBP or PP.[28] Finally, in a recent double-blind therapeutic trial, it has been shown that two-drug regimens may cause the same reduction of MBP and DBP, but with significantly different reductions of PP and SBP (figure 2). This was shown comparing atenolol to a low dose combination of indapamide and perindopril,[32] but not in a comparison of atenolol with the angiotensin II antagonist

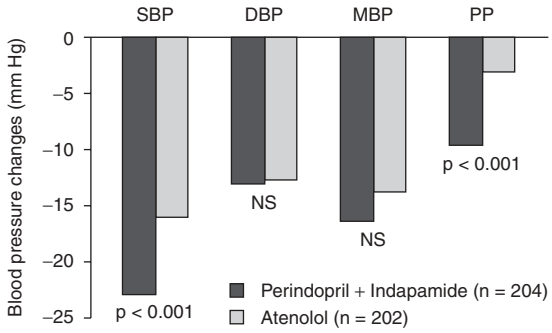

Fig. 2. Changes of SBP, DBP, MBP and PP after treatment for 1 year with atenolol or a perindopril/indapamide combination in hypertensive patients. For the same reduction in DBP, the SBP and PP were more significantly reduced with the combination therapy.[32] **DBP** = diastolic blood pressure; **MBP** = mean blood pressure; **NS** = not significant; **PP** = pulse pressure; **SBP** = systolic blood pressure.

losartan.[33] Such studies confirm in clinical practice the validity of the methodology using PP.

5. Conclusion

In conclusion, this review suggests that the appropriateness and/or utility of PP as an outcome has potentially important implications for the approach to the treatment of cardiovascular diseases. Nevertheless, it is noteworthy that most of the current literature regarding PP contains association studies or secondary analyses of prospective studies, suggesting that at the moment conclusions are suggestive but not definitive. New studies are required to respond to this important question.

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