Pulse Pressure and Pulse Pressure Amplification as Biomarkers in Cardiovascular Disease

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Yi Zhang, Chenhui Tai, Chen Chi, Athanase D. Protogerou, Jacques Blacher, and Michel E. Safar

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Y. Zhang • C. Tai • C. Chi
Department of Cardiology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China
e-mail: yizshcn@gmail.com; taichenhui@gmail.com; chichen1992@qq.com

A.D. Protogerou
Cardiovascular Prevention and Research Unit, Department of Pathophysiology, Medical School, National and Kapodistrian University of Athens, Athens, Greece
e-mail: aprotog@med.uoa.gr

J. Blacher • M.E. Safar (✉)
Diagnosis and Therapeutic Center, Hôtel-Dieu, Paris Descartes University; AP-HP, Paris, France
e-mail: jacques.blacher@htd.aphp.fr; michel.safar@htd.aphp.fr

V.B. Patel, V.R. Preedy (eds.), *Biomarkers in Cardiovascular Disease*, Biomarkers in Disease: Methods, Discoveries and Applications, DOI 10.1007/978-94-007-7678-4_7

Abstract

Recent evidence indicated that pulse pressure and pulse pressure amplification, the ratio or difference between the peripheral and central pulse pressure, might provide prognostic information in patients with cardiovascular diseases. Theoretically, any emerging clinical biomarker should be easy in application, reliable in measurement, predictable in prognosis, and instructive in treatment. Herein, in this chapter, we will focus on the measurement, reference, prognosis, and treatment of pulse pressure and pulse pressure amplification and expound them as biomarkers in cardiovascular disease.

Keywords

Biomarker • Pulse pressure • Pulse pressure amplification • Measurement • Reference • Prognosis • Treatment

Abbreviations

ACE	Angiotensin-converting enzyme
ARB	Angiotensin receptor blocker
AUC	Area under curve
CI	Confidence interval
CKD	Chronic kidney disease
HR	Hazard ratio
SD	Standard deviation
WHO	World Health Organization

Key Facts of Pulse Pressure and Pulse Pressure Amplification

- Pulse pressure is considered as a cardiovascular biomarker since 1990s.
- Pulse pressure amplification, an emerging cardiovascular biomarker, is the ratio or difference between peripheral and central blood pressure.
- Pulse pressure amplification is practical for clinical use, with reliable measurement and established reference system.
- Prognostic value of pulse pressure amplification is proved in various populations, especially in the elderly.
- Angiotensin-converting enzyme inhibitor and angiotensin receptor blocker and calcium channel blocker are effective agents in increasing pulse pressure amplification.

Definitions

Pulse pressure Pulse pressure is a blood pressure component, which is calculated as the difference between systolic and diastolic blood pressure.

Pulse pressure amplification Pulse pressure amplification is considered as a novel cardiovascular biomarker, which is calculated as the ratio or difference between the peripheral and central pulse pressure.

Tonometry-based device Central blood pressure can be measured noninvasively by tonometry-based device, such as SphygmoCor and PulsePen, with applanation tonometry for pulse waveform recording and calibration by brachial blood pressure.

Reference value Reference value contains the one- or two-tail cutoff values, derived from the large-scale measurements, which is used by physicians to identify the abnormal cases in clinical practice.

Prognostic value A biomarker with prognostic value means it can be used to predict prognosis, such as future mortality and events.

Introduction

High blood pressure is the most common and important cardiovascular risk factor and is considered a global public crisis. On April 7, 2013, Professor Margaret Chan, the director of the World Health Organization (WHO), demonstrated that hypertension affected more than one billion people worldwide and led to over nine million deaths per year (WHO report 2013).

In history, as early as the nineteenth century, Riva-Rocci introduced the sphygmomanometer in clinical practice, the first device for assessing arterial blood pressure (Riva-Rocci 1896). During the following century, attention focused on the extreme values of systolic and diastolic blood pressure recorded at the brachial artery. However, diastolic blood pressure fell by the wayside as a predictor, when Franklin SS et al. proved that an elevated diastolic blood pressure lost its prognostic value in subjects over 50 years old from the Framingham study (Franklin et al. 2001). Furthermore, in elderly patients, Franklin SS et al. also indicated that diastolic blood pressure was inversely related to cardiovascular risk (Franklin et al. 1999). Before Franklin, brachial mean blood pressure, together with pulse pressure, made a strong showing as a risk predictor (Darne et al. 1989) but was overtaken by pulse pressure as the best pressure indicator (Sesso et al. 2000; Thomas et al. 2001; Miura et al. 2001; Lewington et al. 2002).

More recently, some studies highlighted the importance of central systolic blood pressure and central pulse pressure as cardiovascular prognostic factors. In theory, central blood pressure is superior to peripheral blood pressure, as a reliable indicator of blood pressure, since it is the real pressure imposed on the left ventricle. In this respect, central blood pressure measurement is of great interest in terms of the clinical application, and some devices for the noninvasive central blood pressure measurement, such as SphygmoCor, were developed (Williams et al. 2006; Waddell

et al. 2001). Moreover, Jankowski et al. provided invasive evidence favoring central over peripheral pulse pressure for risk prediction (Jankowski et al. 2008).

Normally, central blood pressure is lower than peripheral blood pressure, so the difference between peripheral and central blood pressure should be a positive value, known as blood pressure amplification (Nijdam et al. 2008). Moreover, Safar ME et al. and Benetos A et al. all indicated that the disappearance of the blood pressure amplification phenomenon (the lower blood pressure amplification) was a significant predictor of all-cause and cardiovascular mortality, independent of age and other standard confounding factors (Safar et al. 2009; Benetos et al. 2010). Later, other clinical investigations further indicated that the absence of pulse pressure amplification is a significant predictor of cardiovascular mortality in the general population and in the elderly (Benetos et al. 2012; Cho et al. 2013). For instance, in more than 1,100 nursing-home residents over the age of 80 years from the PARTAGE study, it was indicated that reduced pulse pressure amplification was significantly and independently associated with the presence of cardiovascular diseases and was a strong predictor of total and cardiovascular mortality (Benetos et al. 2012).

Theoretically, any emerging biomarker, such as pulse pressure amplification, should be easy in application, reliable in measurement, predictable in prognosis, and instructive in treatment, and it should also provide complementary and independent prognostic value compared with existing biomarkers. In this chapter, we will expound pulse pressure and pulse pressure amplification as new biomarkers in cardiovascular disease.

Pulse Pressure as a Biomarker in Cardiovascular Disease

Pulse pressure, the difference between systolic and diastolic blood pressure, is considered as a reliable indicator of arterial stiffness and as a biomarker of asymptomatic target organ damage, especially in the geriatric population. In history, many clinical investigations indicated the significant association of cardiovascular events and mortality with pulse pressure, and we summarized the major prospective data in Table 1.

In 1994, Madhavan et al. indicated that in 2207 hypertensives, a wide pretreatment pulse pressure was significantly associated with subsequent cardiovascular complications, and the extreme value of diastolic blood pressure, either too high or too low, would lead to a great risk of myocardial infarction, after adjustment for sex, race, age, and previous cardiovascular disease (Madhavan et al. 1994). Fang J et al. indicated that in 5730 hypertensives, after a follow-up of over 5 years, pulse pressure was significantly associated with myocardial infarctions in both untreated patients and all patients, with hazard ratios (HRs) of 1.49 (95 % confidence interval [CI] 1.18–1.89) and of 1.72 (1.47–2.01), respectively (Fang et al. 1995). In 1997, Benetos A. indicated that in 19083 Frenchmen

Table 1 Major prospective investigations on the association of cardiovascular end points with pulse pressure

Investigator, year	Subjects (mean age, years)	Events and mortality	Major findings (hazard ratio (95 % confidence interval))
Madhavan et al. (1994)	2, 207 hypertensives	MI and cardiovascular mortality	A wide pretreatment pulse pressure was associated with subsequent cardiovascular complications in hypertensives
Fang et al. (1995)	5, 730 hypertensives (53)	MI	Pulse pressure was significantly associated with the occurrence of MI in all subjects (1.74 (1.41–2.01))
Benetos et al. (1997)	19, 083 Frenchmen (40–69)	All-cause and cardiovascular mortality	A wide pulse pressure was an independent significant predictor of all-cause, especially coronary mortality
Franklin et al. (1999)	1, 924 subjects (50–79) (Framingham Heart Study)	Coronary heart disease	PP (1.23 (1.16–1.30)) was better than SBP (1.16 (1.11–1.21)) or DBP (1.14 (1.03–1.26)) in predicting CHD risk
Thomas et al. (2008)	69,989 subjects (>50)	Cardiovascular stroke and coronary mortality	Increased PP predicts cardiovascular mortality, acting more on coronary than cerebral vessels

MI myocardial infraction, *PP* pulse pressure, *DBP* diastolic blood pressure, *CHD* coronary heart disease

aged 40–69 years, pulse pressure was an independent and significant predictor of cardiovascular and all-cause mortality (Benetos et al. 1997). The most convincing evidence was from the Framingham Heart Study with over 20-year follow-up, in which 1924 subjects between 50 and 79 years of age with no clinical evidence of coronary heart disease and free of antihypertensive treatment (Franklin et al. 1999). In this study, Franklin SS et al. concluded that higher pulse pressure was a critical indicator of cardiovascular risk, and pulse pressure was superior to systolic and diastolic blood pressure in predicting coronary heart disease with a HR of 1.23 (1.16–1.30) per 10 mmHg.

With those solid evidences, pulse pressure is considered as a critical risk predictor and an asymptomatic target organ damage in cardiovascular disease, especially in patients over 50 years old. Although pulse pressure over 60 mmHg was considered as an asymptomatic target organ damage according to the guideline from the European Society of Hypertension, as far as we know, there is still no clinical trial focusing on pulse pressure control as primary treatment target. Further studies or post hoc analyses are warranted in this field.

Pulse Pressure Amplification as a Biomarker in Cardiovascular Disease

Basic Concept of Central Blood Pressure and Pulse Pressure Amplification

Central blood pressure is the blood pressure in the ascending aorta (Salvi 2012). Many years ago, central blood pressure could only be measured by the invasive method, using catheter-based BP monitor. Nowadays, with the development of tonometry technique and pulse wave analysis, it can be measured noninvasively with tonometry-based devices, and the methodology was validated by the invasive measurement (Papaioannou et al. 2009). From a physiological viewpoint, during the systole, central blood pressure is the pressure that the left ventricle directly confronts, so it affects cardiac afterload and cardiac work and is the main contributor in the development of left ventricular remodeling. During the diastole, central blood pressure influences the coronary blood flow and maintains an adequate subendocardial perfusion (Salvi 2012). So in summary, central blood pressure defines the cardiac work in the systole, whereas in the diastole, it affects the regular blood flow to the ventricular myocardium. However, central blood pressure is pressure dependent or calibration dependent, so, more recently, the ratio of peripheral and central blood pressure, which is independent of pressure measurement or calibration procedure, known as blood pressure amplification, is recognized as a better pressure indicator (Avolio et al. 2009). Then, pulse pressure amplification, the ratio of peripheral and central pulse pressure, is proved as a potential biomarker for arterial stiffness, especially in the geriatric population (Benetos et al. 2012).

Measurements of Central Blood Pressure and Pulse Pressure Amplification

As shown in Fig. 1, peripheral pressure waveform (right panel) is noninvasively recorded by tonometry device, and it is calibrated by the brachial systolic and diastolic blood pressure or the diastolic and mean blood pressure, which are assessed by the brachial blood pressure monitor. Then, the aortic pressure waveform can be transformed by the peripheral pressure waveform via a validated transfer function. This generalized transfer function is derived by applying several mathematical techniques (e.g., time domain or frequency domain analysis) and validated by several clinical investigations. Alternatively (left panel) the central pressure waveform can be directly recorded on carotid artery by tonometry-based devices and then calibrated by the mean and diastolic brachial blood pressure in order to obtain central systolic blood pressure and pulse pressure, since the mean and

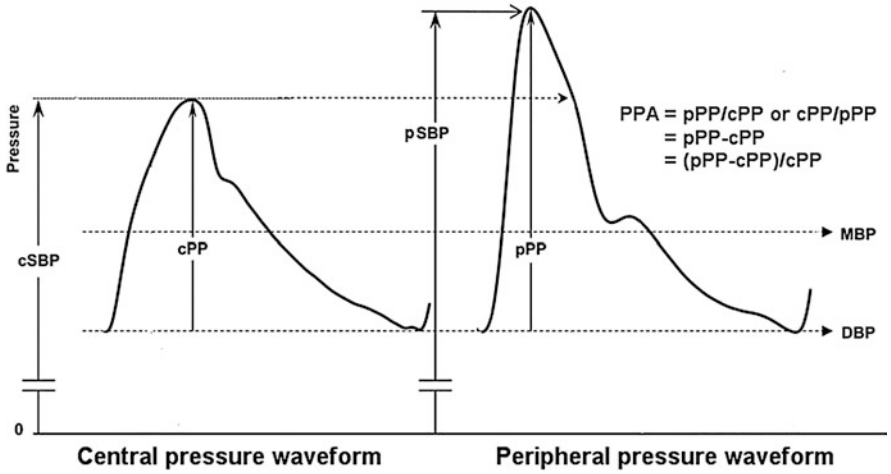

Fig. 1 Measurements on central blood pressure and pulse pressure amplification. Peripheral pressure waveform (*right panel*) is firstly recorded and calibrated by the brachial systolic and diastolic blood pressure. Peripheral mean and diastolic blood pressure are calculated with the area under curve (AUC) method. Central pressure waveform (*left panel*) is recorded on the carotid artery or transformed by the peripheral pressure waveform via a validated transfer function. Central pressure waveform can be calibrated by the mean and diastolic blood pressure in order to obtain central systolic blood pressure and pulse pressure, since the mean and diastolic blood pressure almost remain unaltered in the entire arterial tree. Pulse pressure amplification can be calculated by the ratio of peripheral and central pulse pressure, or the difference in mmHg between peripheral and central pulse pressure, or the difference divided by the central pulse pressure. *pSBP* peripheral systolic blood pressure, *pPP* peripheral pulse pressure, *cSBP* central systolic blood pressure, *cPP* central pulse pressure, *MBP* mean blood pressure, *DBP* diastolic blood pressure, *PPA* pulse pressure amplification

diastolic blood pressure almost remain unaltered in the entire arterial tree (Avolio et al. 2009).

The superiority of the two methodologies (direct carotid recording versus the use of the transfer function) is still under debate.

It is well established that the blood pressure differs markedly between peripheral (brachial) and central arteries (aorta). As the pressure wave travels distally from the heart, a gradual and significant increase of systolic blood pressure and pulse pressure occurs. This phenomenon is called blood pressure amplification and is under extensive investigation, especially the pulse pressure amplification (Avolio et al. 2009). In previous investigations, pulse pressure amplification was calculated by several formulas. Most commonly, it is defined by the ratio of peripheral and central pulse pressure, as indicated in Fig. 1. Alternatively, it can also be expressed as the difference (in mmHg) between peripheral and central pulse pressure or the difference divided by the central pulse pressure (Fig. 1) (McEniery 2008; Segers et al. 2009).

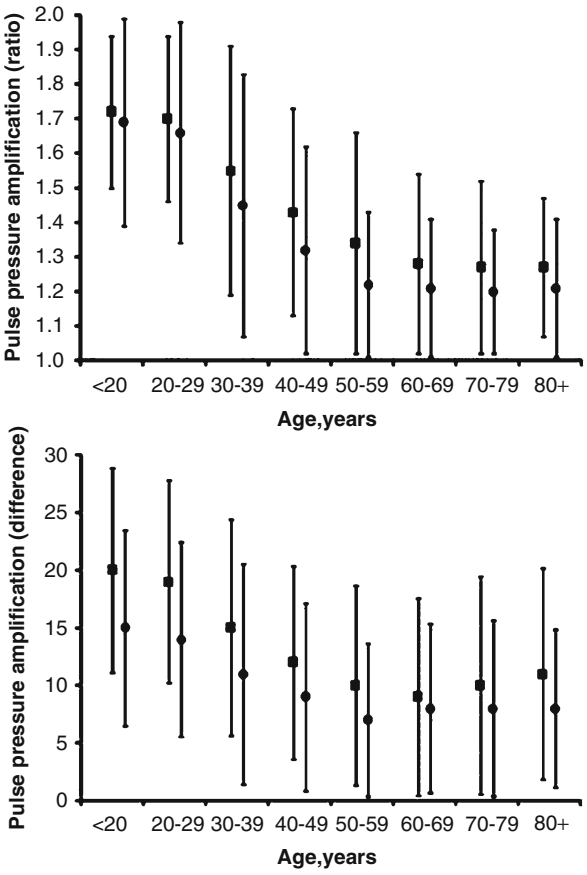

Fig. 2 Reference value of pulse pressure amplification according to age group in men and women. The mean pulse pressure amplification and 95 % confidential interval are expressed as the ratio of peripheral and central pulse pressure (*upper panel*) and the difference between peripheral and central pulse pressure (*lower panel*). Men are indicated as the filled square, and women are indicated as the filled circle (Adapted from McEniery 2008, with permission)

Reference Value of Pulse Pressure Amplification

In the literature, limited data is available regarding the reference value of pulse pressure amplification. In the Anglo-Cardiff Collaborative Trial (ACCT), central blood pressure was determined by the radial pressure waveform with the help of the validated transfer function and calibrated by the brachial systolic and diastolic blood pressure in 5648 participants, and pulse pressure amplification is calculated by the ratio of peripheral and central pulse pressure and by the difference between them. Pulse pressure amplification, expressed by the ratio of peripheral and central pulse pressure, varied from about 1.7 in subjects <20 years old to about 1.2 in subjects >80 years old. The corresponding values for the absolute difference between peripheral and central pulse pressure were 20 mmHg for subjects <20 years old and 7 mmHg for subjects >80 years old (Fig. 2) (McEniery 2008). Recently, a meta-analysis involved 45, 436 subjects with measurements of pulse pressure

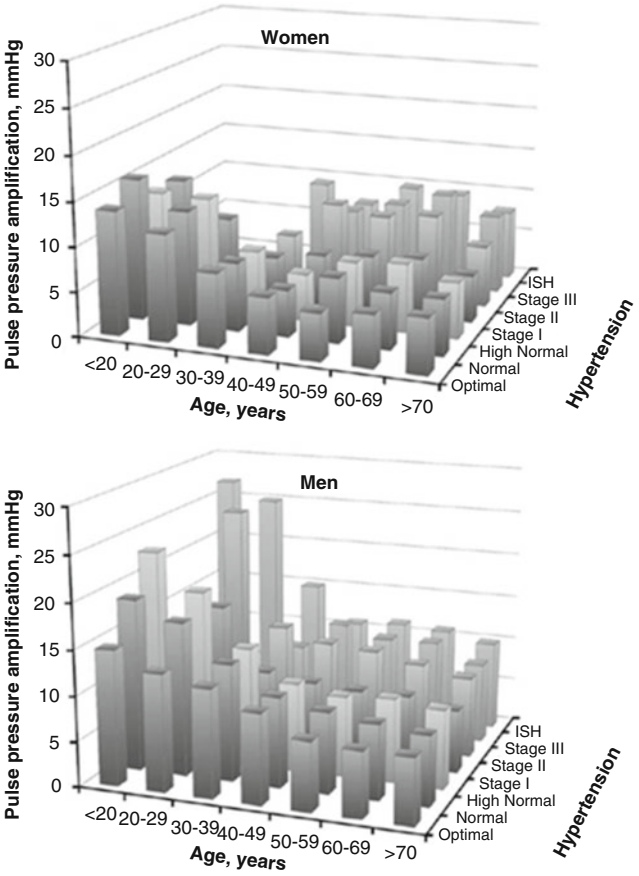

Fig. 3 Pulse pressure amplification stratified by blood pressure category and age in both men and women. Pulse pressure amplification is presented according to age groups and blood pressure categories (optimal blood pressure, normal blood pressure, high normal blood pressure, stage I hypertension, stage II hypertension, stage III hypertension, isolated systolic hypertension). Pulse pressure amplification is calculated as the difference between peripheral and central pulse pressure. *ISH* isolated systolic hypertension (Adapted from Herbert et al. 2014, with permission)

amplification from 77 studies, and most subjects are apparently healthy, without antihypertensive or anti-dyslipidemia therapy and free of overt cardiovascular disease and diabetes (Herbert et al. 2014). As shown in Fig. 3, pulse pressure amplification was stratified by blood pressure category and age in both men and women. It is noteworthy that pulse pressure amplification gradually decreases with age, and the magnitude is greater in men than in women. Moreover, at the similar age and blood pressure level, men had averagely 6.6 mmHg greater pulse pressure amplification than women.

Influencing Factors of Pulse Pressure Amplification

The determinants of pulse pressure amplification are still unclear, or its clinical relevance is still under debate. Cross-sectional data in healthy subjects from the ACCT study (McEniery 2008) and the Asklepios study (Segers et al. 2009) showed that pulse pressure amplification is modulated by vascular properties, such as large artery stiffness, peripheral resistance, and mainly pressure wave reflections, as well as by heart rate. The principal mechanism of these factors influencing pulse pressure amplification largely relied on the "timing–synchronization" of the forward and reflected pressure waves. In addition, classical non-modifiable (i.e., age and sex) and modifiable cardiovascular risk factors (i.e., high blood pressure, high plasma glucose, hypercholesterolemia, and smoking) or established cardiovascular disease are also significantly associated with reduced pulse pressure amplification in observational studies (Wilkinson et al. 2001; McEniery 2005). These factors may accelerate biological vascular ageing, which is per se the main modulator of large artery stiffness and wave reflections.

From this point of view, pulse pressure amplification, integrating other cardiovascular risk factors and global arterial properties, could serve as a biomarker of cardiovascular risk (Benetos et al. 2012). The available data imply that pulse pressure amplification is not just a mathematical expression but carries additional physiological information, potentially above that of central and peripheral blood pressure alone.

Prognostic Value of Pulse Pressure Amplification

In the literature, most prospective data indicated that pulse pressure amplification, expressed by the ratio or the difference between the peripheral and central pulse pressure, was significantly associated with cardiovascular events and mortality. As shown in Table 2, in 2008, Nijdam ME et al. indicated that in men between 40 and 80 years of age, a higher pulse pressure amplification was significantly associated with a better cardiovascular risk profile, a reduced pulse wave velocity, a reduced common carotid intima-media thickness, and a lower Framingham risk score of coronary heart disease, after adjustment for age, blood pressure level, body height, and heart rate (Nijdam et al. 2008). However, in 2010, in general population from the Framingham Heart Study, pulse pressure amplification failed to provide independent predictive information for major cardiovascular events (HR, 0.86 [0.19, 3.82]) (Mitchell et al. 2010). On the contrary, Benetos A et al. indicated that in a large French cohort at a mean age of 40.4 years old ($n = 125, 151$), 1 standard deviation (SD) increase in brachial pulse pressure was significantly associated with cardiovascular and all-cause mortality, with HRs of 1.17 and 1.13, respectively; the corresponding HRs for the estimated carotid pulse pressure were 1.20 and 1.17, respectively, while the pulse pressure amplification exhibited the highest HRs as 1.30 and 1.19 for cardiovascular and all-cause mortality, respectively (Benetos et al. 2010).

Table 2 Major investigations on the association of cardiovascular outcomes with pulse pressure amplification

Investigator, year	Participants (mean age, years)	Measurement of PPA	Events and mortality	Major findings
Nijdam et al. (2008)	400 men (40–80)	bPP/cPP	10-year risk of CHD using Framingham score	A higher PPA reflected a lower CV risk in men between 40 and 80 years of age
Benetos (2010)	125, 151 Frenchmen (40.4)	Estimated cPP/bPP	All-cause and CV mortality	PPA was a strong risk predictor with a HR of 1.22 and 1.41 for CV and all-cause mortality, respectively
Mitchell et al. (2010)	2,232 patients (63 ± 12) (Framingham Heart Study)	bPP/cPP	CV events	PPA was not significantly associated with CV events ($P = 0.84$)
Benetos et al. (2012)	1, 126 patients in nursing home (88 ± 5) (PARTAGE study)	(bPP-cPP)/cPP	All-cause mortality major CV events	A 10 % increase in PPA was associated with a 24 % decrease in total mortality and a 17 % decrease in major CV events
Regnault et al. (2012)	72, 437 men (41 ± 11) 52, 714 women (39.5 ± 11.6)	bPP/cPP	Age-related CV mortality	In postmenopausal women, PPA contributed to the significant increase in CV risk
Cho et al. (2013)	80 patients undergoing CAG (62.7 ± 10.1)	cPP/bPP	Extent of CHD	PPA was related to the severity of CAD, particularly in patients <65 years old
Wassertheureu et al. (2014)	135 patients with CKD 2 to 4 (60 ± 14.9)	bPP/cPP	Renal end points all-cause mortality	Patients with CKD stage 4 and low PPA had the highest risk for renal end points, adjusted for age and proteinuria

PPA pulse pressure amplification, *bPP* brachial pulse pressure, *cPP* central pulse pressure, *CV* cardiovascular, *CAD* coronary angiograph, *CHD* coronary heart disease, *CKD* chronic kidney disease

The most convincing data were derived from the PARTAGE study, a longitudinal study with a mean follow-up of 2 years, in which 1126 elderly subjects over 80 years old, living in the nursing home, were included (Benetos et al. 2012). In this study, Benetos A et al. indicated that a 10 % increase in pulse pressure amplification was significantly and independently associated with a 24 % decrease in total mortality

and a 17 % decrease in major cardiovascular events, after adjustment for other potential confounders. Regnault V et al. also found that pulse pressure amplification was highly predictive of differences in the age-related cardiovascular mortality in men and women, separately, after adjustment for known cardiovascular risk factors (Regnault et al. 2012).

Moreover, some investigators also reported that pulse pressure amplification was also a significant predictor of severity of coronary heart disease in patients undergoing coronary angiograph. For instance, Cho SW et al. (Cho et al. 2013) indicated that after adjustment for known risk factors, pulse pressure amplification was significantly related to the severity (evaluated by the Gensini score) of coronary heart disease. In addition, Wassertheurer S et al. assessed pulse pressure amplification in 135 patients with chronic kidney disease (CKD) stage 2 to 4 and 89 controls, in which pulse pressure amplification was reduced in CKD patients as compared with the control and significantly and independently associated with the decline in renal function and mortality, after adjustment for age and proteinuria (Wassertheurer et al. 2014).

In summary, pulse pressure amplification, expressed by the ratio or difference between peripheral and central pulse pressure, predicts cardiovascular events and mortality in most studies, especially in the elderly. Assessment of this parameter could help in risk assessment and improve diagnostic and therapeutic strategies in those patients.

Pulse Pressure Amplification and Treatment

Although it seems well established that pulse pressure amplification is a significant predictor of cardiovascular events and mortality, data are scarce regarding the effect of cardiovascular agents on it. In Table 3, major investigations in this field with regard to principal cardiovascular agents, such as adrenoceptor-β blocker, calcium channel blocker, angiotensin-converting enzyme (ACE) inhibitor, and angiotensin receptor blocker (ARB), were summarized.

As to adrenoceptor-β blocker, the first direct evidence came from a subgroup analysis in the REASON study ($n = 354$) (Asmar et al. 2001). In this study, Asmar RG et al. indicated that after a 12-month treatment, atenolol exhibited a more pronounced antihypertensive effect on peripheral blood pressure than central blood pressure, and, consequently, pulse pressure amplification was significantly lower in the atenolol treatment arm, as compared with placebo. Similarly, in a small-sample, randomized, double-blinded study in untreated hypertensives at middle age, Dhakam et al. also indicated that pulse pressure amplification was significantly reduced after 6 weeks of the atenolol treatment (Dhakam et al. 2006).

London G et al. investigated the long-term antihypertensive effect of nitrendipine on peripheral and central blood pressure, in 24 patients with end-stage renal disease. Data indicated that nitrendipine significantly reduced both peripheral and central blood pressure (London et al. 1994). However, the effect on central pulse pressure was more prominent than peripheral pulse pressure,

Table 3 Major investigations on treatment of pulse pressure amplification

Agent, dosage	Comparator	Investigator, year	Duration	Participants (mean age, years)	Measurement of PPA	PPA		
						Agent	Comparator	*P*
Adrenoceptor-β blockers								
Atenolol, 5 mg	Baseline	Asmar et al. (2001)	12 months	354 untreated hypertensives (53)	bPP/cPP	1.09	1.22	<0.001
Atenolol, 5 mg	Baseline	Dhakam et al. (2006)	6 weeks	21 untreated hypertensives (51)	bPP/cPP	1.21	1.38	<0.001
Atenolol, 5 mg	Placebo	Dhakam et al. (2008)	5 weeks	16 low-risk uncontrolled hypertensives (70)	bPP/cPP	1.2	1.39	<0.001
Nebivolol, 5 mg								
Calcium channel blockers								
Nitrendipine, 20/40 mg	Baseline	London et al. (1994)	12 months	24 patients with ESRD (53)	bPP/cPP	1.13	1	<0.01
Angiotensin-converting enzyme inhibitor and angiotensin receptor blocker								
Perindopril, 2/4 mg tiw	Baseline	London et al. (1994)	12 months	24 patients with ESRD (53)	bPP/cPP	1.1	1.02	<0.01
Eprosartan, 400 mg	Baseline	Dhakam et al. (2006)	6 weeks	21 untreated hypertensives (51)	bPP/cPP	1.42	1.38	<0.001
Quinapril, 20 mg	Placebo	Aznaouridis et al. (2007)	2 h	100 hypertensives (53)	bPP/cPP	9.8 ± 4.4	8.8 ± 7.6	NS
Captopril, 25 mg						11.4 ± 5.7		
Telmisartan, 80 mg						11.4 ± 5.7		

PPA pulse pressure amplification, *bPP* brachial pulse pressure, *cPP* central pulse pressure, *ESRD* end-stage renal dysfunction, *NS* nonsignificant

and pulse pressure amplification was therefore significantly increased after a 12-month nitrendipine treatment.

In the literature, ACE inhibitor and ARB are more extensively studied. In a randomized and double-blind clinical investigation with placebo run in and two parallel active treatment groups, London et al. indicated that in 24 patients with end-stage renal disease, perindopril significantly reduced patients' pulse pressure amplification after a 12-month treatment (London et al. 1994). Similarly, Dhakam et al. also reported that in 21 untreated hypertensives (mean age, 51 years), eprosartan significantly reduced peripheral and central blood pressure but significantly increased patients' pulse pressure amplification (Dhakam 2006). Aznaouridis K et al. (Aznaouridis et al. 2007) also investigated the transient antihypertensive effect of ACE inhibitor and ARB on pulse pressure amplification, namely, captopril 25 mg and quinapril 20 mg and telmisartan 80 mg, but without significant change.

In summary, clinical studies favor calcium channel blocker, ACE inhibitor, and ARB in terms of pulse pressure amplification increment. However, adrenoceptor-β blocker, mainly atenolol, decreases pulse pressure amplification, which may be largely attributed to the associated bradycardia and the consequent resynchronization of the reflected pressure wave relatively earlier in the systolic phase.

Conclusion

Pulse pressure has been recognized as an established cardiovascular biomarker for decades and was proved in the Framingham Heart Study. Recent data indicated that pulse pressure amplification, the ratio or difference between peripheral and central pulse pressure, might provide prognostic value in patients with cardiovascular diseases, especially in the elderly. Normally, it requires at least four characteristics for any emerging biomarker to be a clinical practical one, namely high-reproducibility measurement, reference for clinical use, incremental prognostic value, and guidance in treatment. Pulse pressure amplification, a pressure-independent parameter reflecting patients' arterial stiffness and other cardiovascular risks, could be reproducibly measured by the noninvasive tonometry-based device, and the reference value has been set to screen for the abnormal in clinical practice. Most population studies and clinical data indicated that pulse pressure amplification could provide independent prognostic value for cardiovascular and all-cause mortality and other renal and cardiac outcomes. In treatment, ACE inhibitor and ARB and calcium channel blocker are effective in increasing pulse pressure amplification, whereas adrenoceptor-β blocker may act in the opposite direction. In summary, pulse pressure amplification is an emerging biomarker in cardiovascular disease but is still on the way to be a reliable and practical one. Further studies are still warranted to ensure the incremental prognostic value of pulse pressure amplification in various populations. Besides, whether the increase in pulse pressure amplification by cardiovascular agents can eventually result in patients' prognostic

benefit, it is still uncertain and is the most important issue to be proved in future investigations.

Potential Applications to Prognosis, Other Diseases, or Conditions

Pulse pressure, an established cardiovascular biomarker, indicates the severity of patients' arterial stiffness and is considered as an asymptomatic target organ damage in various populations, especially those over 50 years old. Pulse pressure amplification, another emerging indicator of arterial stiffness and a pressure-independent index, potentially provide incremental prognostic information over known cardiovascular risk factors. However, controversy exists in the literature. In general population, such as in the Framingham Heart Study, pulse pressure amplification failed to provide independent predictive value for cardiovascular and all-cause mortality. On the contrary, in the geriatric population, like the PARTAGE population, pulse pressure amplification served as a strong and independent death predictor. It is hypothesized that pulse pressure amplification, like pulse pressure, favors the elderly and high-risk population, with regard to the death and event prediction. Further studies are still warranted to prove the incremental prognostic significance of pulse pressure amplification and enlarge its clinical application.

Summary Points

- Pulse pressure is an established biomarker in cardiovascular disease, especially in patients over 50 years old.
- Pulse pressure amplification, a pressure-independent biomarker, can be reproducibly measured by noninvasive tonometry-based devices, and its reference has been set for clinical use.
- Pulse pressure amplification, integrating other cardiovascular risk and global arterial properties, is a cardiovascular biomarker.
- Pulse pressure amplification acts as an independent predictor of cardiovascular and all-cause mortality and other renal and cardiac outcomes.
- Angiotensin-converting enzyme inhibitor and angiotensin receptor blocker and calcium channel blocker increase pulse pressure amplification, but adrenoceptor-β blocker deceases.

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