Pulse Wave Analysis and Pulse Wave Velocity
— A Review of Blood Pressure Interpretation
100 Years After Korotkov —-

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The pulsatile component of blood pressure (ie, pulse pressure) has received considerable attention as an important risk factor for cardiovascular disease. In particular, central blood pressure measurements in the ascending aorta or in the carotid artery are expected to be more useful than conventional brachial pressure measurements for predicting cardiovascular events because central pressure, not the brachial pressure, is the pressure that target organs encounter. Due to wave reflection, the blood pressure in the upper limb does not represent the central blood pressure; therefore, leading researchers have enthusiastically promoted a noninvasive method of measuring central blood pressure and the resulting aortic stiffness. Until now, there has been an increasing body of evidence to support the accuracy and superiority of central blood pressure measurements as well as the assessment of aortic properties over classical brachial pressure measurements. In this review, the information regarding these “central” indices derived from 2 main methods, namely “pulse wave analysis” and “pulse wave velocity”, for the application of central blood pressure measurements and arterial stiffness to clinical study and practice, has been summarized. (Circ J 2006; 70: 1231–1239)

Key Words: Arterial stiffness; Central blood pressure measurement; Wave reflection

Increasingly, in recent times, the value of the cuff sphygmomanometer that provides arterial pressures (brachial systolic and diastolic pressure) is coming under question. The concerns extend well beyond the familiar issue of “white coat” hypertension, home and 24-h blood pressure recordings, and the phase-out of mercury based instruments. These concerns relate to the inaccuracy of all cuff devices for measuring pressure within the brachial artery, the difference between pressures in the brachial artery and central aorta, and the interpretation of systolic, diastolic, mean and pulse pressure (PP).1

The present questions can be seen in context when one considers the history of hypertensive disease and its assessment by clinicians over the past 2 centuries. Richard Bright was the first to study “high arterial tension” and its relationship with kidney disease, cardiac failure and stroke.2 His name that “Systolic blood pressure represents the maximum force of the heart, and diastolic blood pressure measures the resistance the heart has to overcome.”—that is, that elevated diastolic pressure was bad but elevated systolic pressure was good.3 Such a view became entrenched and was widely held until initially questioned by the Framingham results,4 then contradicted by the US NIH’s Systolic Hypertension in the Elderly Project (SHEP).5 Up until 1991, studies on arterial pressure had consistently reported on the positive relationship between cardiovascular events and diastolic pressure (Fig 1).6–18

There is good reason why diastolic pressure was preferred to systolic from the time of Korotkov until the SHEP results were published in 1991.6 This was the period when hypertensive disease was rife and unchecked—when no effective therapy was available and the vicious circle of hypertension regularly resulted in the malignant phase with early death from stroke, or renal or heart failure.7 Franklin D. Roosevelt was one victim with a pre-stroke pressure recorded at 250/160.8 The reported studies in Fig 1 related largely to this era.6–18

The change in emphasis from diastolic to systolic pres-
sure occurred in the latter part of this era, as elevated systolic arterial pressure was recognized more frequently before organ damage was evident, and the vicious circle was broken through the use of effective antihypertensive therapies. Another type of hypertensive disease then became evident as isolated systolic hypertension. This now dominates clinical practice. In modern societies, diastolic hypertension, the dominant disease of the early to mid-20th century, has virtually been conquered.

The modern studies reflect this view. The most recent Framingham analysis on the topic shows that cardiovascular events are directly related to systolic but not diastolic pressure in older subjects, and the study concluded that for any given systolic pressure, events are inversely related to diastolic pressure (Fig 2). These results, which indicate increased PP as an important independent risk factor for cardiovascular disease, have been confirmed from analysis of recent European, US and Chinese studies (Fig 3). There is not complete agreement on these views at this time. This difference of opinion is related to the different facets of the relationships between diastolic blood pressure and the relative risk of cardiovascular events, as depicted in Figs 1 and 2. On the basis of more must be better, the influential Prospective Studies Collaboration Group reported the superiority of diastolic over systolic pressure in the assessment of cardiovascular events in one million subjects. In this study, there was no relationship between PP and events. Multiple queries were raised about the findings in this study.

Fig 1. Relative risks of coronary heart disease (CHD) by diastolic blood pressure (DBP) in 9 studies (Merit Screeners, Chicago Heart Association, Whitehall, Puerto Rico, Honolulu, LRC Prevalence, Framingham, Western Electric and People’s Gas). Patients were divided into 5 categories according to the baseline DBP as follows: category 1, DBP ≤79 mmHg; category 2, 80–89 mmHg; category 3, 90–99 mmHg; category 4, 100–109 mmHg; category 5, DBP ≥110 mmHg. Reproduced from MacMahon et al.

Fig 2. Joint influences of systolic blood pressure (SBP) and diastolic blood pressure (DBP) on coronary heart disease (CHD) risk. CHD Hazard Ratios (HRs) were determined from level of SBP within SBP groups. HRs were set to a reference value of 1.0 for SBP of 130 mmHg and DBP of 80 mmHg and are plotted for SBP values of 110, 130, 150 and 170 mmHg, respectively. All estimates were adjusted for age, sex, body mass index, cigarettes smoked per day, glucose intolerance and total cholesterol/HDL. Reproduced from Franklin et al.
subsequent Lancet correspondence. The study was a meta-analysis of 61 prospective studies, most of which had been conducted before the era of modern medical therapy. The participants in these early studies were younger hypertensives and few of them had reached the age at which increasing arterial stiffness had become the dominant cause of elevated blood pressure and cardiovascular events. It is clear that these studies failed to define the risk of an individual currently diagnosed with hypertension. The Framingham study group suggested that diastolic blood pressure was the best predictor of cardiovascular disease in subjects under 40 years of age; however, for people over 60 years old, PP was the best predictor. These findings can be explained on the basis of a strong amplification of the brachial PP in young subjects, a phenomenon whose extreme manifestation is “spurious systolic hypertension” in youth, and whose central systolic and central PP are normal!

These points raised questions on the use of the century-old cuff sphygmomanometer and explain the quest for other more modern methods that may be used in clinical practice. Instrumentation has improved this century but has not yet been applied to clinical assessment of arterial pressure widely. Ironically, the useful supplementary methods, pulse wave analysis (PWA) and pulse wave velocity (PWV) measurement, are variants of those used by Mackenzie, Lewis and others before introduction of the now ubiquitous cuff. These can provide information on arterial stiffening, early wave reflection and central blood pressure—the predominant problems of aging and of isolated systolic hypertension—and are based on pathophysiological and clinical studies on arterial elasticity that were commenced in the nineteenth century.

Fig 4. Explanation of the genesis of aortic pressure waveform, and the pressure amplification at an arterial branch. Backward pressure wave (Pr) reflected from the branch is superimposed with forward pressure wave (Pi) from the heart to generate the aortic pressure wave [P=Pi+Pr]. Incident pressure in the parent artery (Pi) is amplified by the impedance discontinuity. [P1=P2=Pi+Pr].

Fig 5. Timing of wave reflection alters the degree of pressure amplification. The figure shows at left, pressure waves recorded in the radial artery by applanation tonometry in a young subject (Above) and old subject (Below); at right are the pressure waves synthesized for the ascending aorta using the SphygmoCor® system in the young (Above) and old (Below) subject. Arrows show the merging points (inflection points) of a pressure wave from the heart and a reflected pressure wave that is the summation of the echo waves from peripheral reflection sites. In youth, wave reflection cannot contribute the value of pulse pressure (PP) both in the aorta and the brachial artery because wave reflection returns at late systole or early diastole (upper panel; high amplification). In contrast, wave reflection returns during early systole and augment the aortic PP, but not brachial PP in the elderly (lower panel; low amplification). BP, blood pressure.
New findings regarding the pulsatile components of brachial blood pressure (systolic blood pressure and PP) obtained by several prospective studies have highlighted non-invasive central pressure measurements for 2 reasons. First, just the central pressure, not the brachial pressure, directly affects the target organs. Second, the brachial pressure does not always represent the central pressure. In young adults, the amplitude of the brachial or radial pressure pulse may be 50% greater than that in the ascending aorta, whereas these pressures are of nearly equal magnitudes in the elderly.34 This difference between the young and elderly can be readily explained on the basis of wave reflection.

Wave Reflection

The forward pressure wave in an artery, transmitted from the central aorta, is reflected back (wave reflection) and amplified toward the periphery at any point of impedance discontinuity, such as arterial branching and arterial-arteriolar junctions (Fig 4).1,35 High-resistance arterioles are considered to be the major sites of wave reflection in the circulatory system; however, individual reflected waves collectively behave like a single reflected wave arising from one functional reflection site, which appears from the proximal thoracic aorta to be near the termination of the aorta in the abdomen. As a result, the pressure waveform recorded in the ascending aorta (or brachial artery) can be described as the sum of the forward pressure wave generated by the heart and the backward (forward in the brachial artery) reflected pressure wave from the body.

The difference in pressure amplification between the young and elderly in the upper-limb artery depends mainly on the different timing of the effect of the wave reflection on the central aortic pressure and on the upper limb artery pressure (Fig 5).1 In the elderly, the reflected pressure wave from the body returns during early systole in the ascending aorta due to the arterial stiffness and augments the aortic PP to a similar degree as the brachial (low amplification). In contrast, in the young, wave reflection affects neither the aortic PP nor the brachial PP because the reflected pressure wave returns during late systole or early diastole in the artery. Therefore, it cannot contribute to an increase in the aortic PP, and consequently results in high amplification.

Pressure amplification also depends on the arterial impedance in the transmission line; however, the influence of this factor has been reported to be small, which relates to the lack of significant changes in the elastic properties of the upper limb arteries with aging.36,37

There is little pressure amplification between the central aortic and upper limb arteries in patients with degenerative cardiovascular disease. However, amplification increases in subjects with heart failure, with the administration of
vasodilator drugs, in tachycardia, and in shock1.

The augmentation index (AIx) is a representative surrogate of wave reflection and is defined as augmented pressure (magnitude of wave reflection) divided by PP (Fig 6). This index had been introduced and used only in invasive hemodynamic studies.38 Fujii et al, for the first time, applied applanation tonometry to the non-invasive measurement of carotid AIx in clinical studies.39 And, at present, PWA using the mathematical method conventionally used for deconvolution has made it possible to estimate the wave reflection in the aorta non-invasively and to generate central blood pressure from radial pressure waveforms with reasonable accuracy.

Generalized Transfer Function: The Principle of PWA

It is a well-known fact that any periodic wave can be divided into a set of sinusoidal waves, called the Fourier series, whose frequencies are all integral multiples of the frequency of repetition of the wave.40 Amplification of the central pressure, using Fourier analysis, is best expressed as the transfer function, where amplification between 2 sites is plotted in terms of amplitude and phase as a function of frequency or harmonic of the wave. In 1970, O'Rourke applied the transfer function to a relationship between central aortic and brachial artery pressure in order to explain the difference in upper-limb pressure waves in aortic valve disease and atrial fibrillation.41 Lasance subsequently published this subject in a large group studied at cardiac catheterization.42 The transfer functions that he reported in 68 patients were almost the same despite their differences in age, sex, size and clinical status.

In 1993, these findings returned to prominence as being possible methods by which to estimate the central aortic pressure waveforms from the non-invasively measured upper-limb pressure waveforms. Karamanoglu et al showed that each transfer function between the central aorta and the brachial artery is also consistent among subjects with coronary artery disease.43 They reanalyzed published data and found no significantly different patterns in radial-to- or brachial-to-ascending aortic transfer function among 27 published patients and among 14 patients in their measurements under different conditions (Fig 7). The consistencies among individual transfer functions are in agreement with multiple studies that had demonstrated little change in the elastic properties of the upper limb arteries with aging and hypertension.36,37,44 Theoretically, the transfer function of the transmission line and the contour of the input pressure wave determine the output pressure wave; this, along with the consistencies among individual transfer functions, implies that only the shape of the input pressure waves in the aorta (aortic pressure waveform) is a major determinant of the shape of the output pressure waveforms in the upper-limb arteries in different individuals under different conditions. Furthermore, there is a possibility that one can reconstruct
accurate aortic pressure waveforms from the upper-limb pressure wave using the averaged transfer function. They named the averaged transfer function as the generalized transfer function and showed that it accurately estimated the central systolic blood pressure (difference, 2.4±1.0mmHg).43 The central aortic measurements using a radial pressure waveform and the generalized transfer function (ie, PWA) have been validated by many studies including drug administrations and are regarded as a preferred method for non-invasive central blood pressure estimation.45–47 Fig 8 shows a representative trace of the radial pressure waveform recorded using high fidelity applanation tonometry and the reconstructed aortic pressure waveform using the generalized transfer function in young and old subjects. PWA is now commercially available (SphygmoCor System; AtCor Medical, Sydney), and has been approved by the FDA for this purpose.

Prognostic Value of Central Blood Pressure and AIx

In spite of the method guaranteed to work based on its principle and many validation studies for the non-invasive aortic pressure measurement using the generalized transfer function, there have been a relatively small number of prospective studies using PWA, compared with those using PWV.

Safar et al reported that carotid PP is an independent risk factor for all-cause mortality in patients with end-stage renal disease (ESRD)48 They also indicated that the Alx derived from the carotid pulse is the major predictor for all-cause mortality in patients with ESRD49 Asmar et al showed that the superior effect of diuretic/angiotensin converting enzyme inhibitor combination on left ventricular hypertrophy was associated with greater effects on the aortic AIx and aortic PP estimated by PWA50–52 Weber et al reported the strong and independent association between the aortic AIx also estimated by PWA, and the presence of coronary artery disease, and the prognosis after percutaneous coronary interventions53,54.

We prefer PWA to the conventional analysis of carotid pressure waveforms due to better reproducibility, less influence on heart rate (excitation of baroreceptors), considerably better patient acceptance (carotid procedure often causes gagging and coughing) and reduced risk of dislodging carotid plaque.1,55 Based on these advantages over carotid analysis, several population studies have adopted PWA for measuring central pressure indices; and the outcomes of some of these recent studies have been published56,57.

PWV

Widened PP is a manifestation of arterial stiffness; therefore, it is natural for researchers to pursue studies on the relationship between arterial stiffness and the outcome for patients with cardiovascular disease. There have been reports on the numerous indices of arterial stiffness; however, no single index has proved superior to the others and all have problems in their measurements and interpretations. Of these indices, PWV is the most frequently used index in prospective studies.

Methodology of PWV

PWV is the measurement of the speed of the pressure waves that travel along the arterial segments (Fig 9).1 The theoretical basis of this measurement depends on the Moens-Korteweg equation; PWV = \sqrt{(\text{Young's modulus} \times \frac{h}{2r})}, where \(h\) is the density of blood, \(\frac{h}{2r}\) is the thickness/diameter of the artery. Young’s modulus is the physical parameter that represents the stiffness of elastic materials.

In practice, PWV was calculated as the distance/traveling time of the wave between 2 measuring sites of the pulse. In an invasive, experimental study, PWV can be measured between the proximal and distal sites in the same artery in the human body.
same line (eg, aorta). However, in a non-invasive, clinical study, the 2 measurement sites should lie on a peripheral artery that can be palpated from the body surface (usually between carotid and femoral arteries for aortic PWV, carotid and brachial arteries for upper-arm PWV, carotid and radial arteries for arm PWV, and femoral and tibial arteries for leg PWV); strictly speaking, these sites do not always lie in the same line of the pulse travel. This technical limitation in the measurement is the main problem with this method.58

In addition to age, atherosclerosis and arteriosclerosis, PWV also increases with an increase in blood pressure, depending upon the elastic nature of the vascular wall, including Young’s modulus. This is the second problem with PWV measurements. One has to exclude the effects of blood pressure changes before estimating the real effects on the vascular properties itself.58 In spite of these limitations, the measurement of the PWV is being used increasingly because of the simplicity of the principle underlying this method. PWV is not influenced by wave reflection.

**Water-Hammer Formula**

Characteristic impedance (Zc) is another valuable index of arterial stiffness, which is described as the ratio of PP and the maximum flow velocity (max F) in the absence of wave reflection. When PWV and Zc are expressed as cm/s and dyne-second/cm², respectively, the following equation is obtained; $Zc = \frac{1.330 \times PP (\text{mmHg})}{\text{max F (cm/s)}} = \frac{\text{PWV} \times \frac{\text{max F (cm/s)}}{\text{PWV}}}{1.05}$. This is called the water-hammer formula, which directly relates the PWV and the pressure and flow phenominal.

**Prognostic Value of PWV**

PWV was first identified as an independent risk factor for cardiovascular diseases in a prospective study conducted in France in 1999 that included patients with ESRD.59 In this study, the odds ratio for the subjects with PWV ≥12 m/s was 5.4 when compared with the subjects with PWV ≤9.4 m/s for all-cause mortality. This cohort study was followed by another article from the same institute, which also validated the prospective value of PWV.60 Patients with ESRD on hemodialysis are known to have a higher mortality and morbidity than those without ESRD; therefore, there was a considerable amount of concern regarding the predictive value of PWV for cardiovascular diseases. However, recent cohort studies confirmed the prognostic value of PWV in general clinical settings.61–67

Another issue regarding PWV is whether the prognostic value of PWV is merely based on the coexisting potential cardiovascular diseases or whether a high PWV really precedes the cardiovascular disease. Several studies have now implied the possibility of both being true. Cruickshank et al suggested the possibility of PWV being the integrated index of vascular risk factors (eg, duration of hypertension or diabetes), which could precede the cardiovascular disease. On the contrary, subjects with overt cardiovascular diseases have a high PWV.58

**Perspectives**

Apart from the evidence obtained by the mass-population study, another problem to be resolved is that of the availability of the 2 methods in clinical settings. Physicians cannot easily obtain PWA and PWV measurements compared with conventional blood pressure measurement. These measurements require special apparatus and trained operators as well as other new medical techniques. They usually require a patient to lie in the supine position for the measurements. In spite of these shortcomings, PWA and PWV will be necessary tools for a cardiovascular physician when the efficacy of the methods is established in a large-scale population study, and the usefulness of the measurement becomes clear in clinical settings.

Multiple studies in normal subjects have shown a progressive increase in aortic PWV (AoPWV) with age, indicating aortic degeneration and stiffening. Such an increase is accentuated in patients with hypertension and ischemic heart disease. Studies have also shown an increase in the late systolic augmentation (Alx) of radial, carotid and aortic pressure waveforms with an increase in age. In contrast, preliminary Framingham data, while confirming the age-related increase in AoPWV, shows little age-related increase in carotid Alx. Adj et al reported that the reduced increase in Alx in hypertensive patients might be attributable to their routine medication with multiple vasoactive drugs. They also pointed out that Alx is easily modified by drug therapy; however, PWV is not. Alx is also dependent on the flow wave contour, and may not rise with age if there is relative reduction in late systolic flow. These points imply that Alx and PWV measurements have different roles in the clinical settings. Using PWV measurements, a clinician can gauge arterial stiffness, which is reflective of the history of patient’s illness, and can assess the effect of drug therapy in persons with normal ventricular ejection by measuring aortic Alx. A decreased Alx should lead to a deceleration in the process of vascular stiffening.

The second issue that remains unresolved is the mechanism by which these 2 indices have an impact on the cardiovascular system. A vicious circle of large arterial disease is proposed (Fig 10), in which high central PP causes aortic dilation and stiffening via elastin fiber fracture. This theory is based on engineering principles and has been supported by many observation studies in humans; however, it has not been proved directly by experimental or human studies because elastic fracture needs 800 million pulsatile stretches over 20 years in elastic arteries. In addition, it is also unclear that this theory could be applied to muscular arteries; for example, coronary artery and peripheral arteries in target organs. Recent studies suggest that PP is associated with plaque rupture in coronary artery, and is transmitted much deeper into the microcirculation than was previously believed; however, further investigations should be conducted on the pathophysiology of arterial stiffness.

**Conclusion**

Modern technology has brought about the powerful tools to evaluate the aortic hemodynamics and central arterial stiffness into clinical medicine. Even though several issues remain unresolved, the new methods have the potential to innovate cardiovascular study and practice, as did the cuff sphygmanometer 100 years ago.

Ongoing and future prospective studies with PWA and PWV will provide us with new strategies for the treatment of cardiovascular disease and hopefully they, and this review, will help cardiovascular physicians seize the opportunity to use these new methods in their clinical study and practice.
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