An updated clinical primer on large artery mechanics: implications of pulse waveform analysis and arterial tonometry

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Purpose of review

The use of pulse wave analysis with arterial tonometry has accelerated over the last year. Despite approval from the US Food and Drug Administration in 2001 on the use of generalized transfer function to generate the central (aortic) pressure wave from the radial waveform, this technique is still questioned. This review summarizes major findings on (a) value of arterial tonometry in determining indices of cardiovascular function, (b) use of these indices in outcome and drug studies, (c) relevance to major trials on blood pressure reduction.

Recent findings

Pulse pressure has emerged as a better predictor of cardiac ischemic events than systolic, diastolic, and mean brachial pressure. Central systolic and pulse pressure and augmentation index have shown an even better relation with cardiovascular events and with outcomes. The claim by specific angiotensin-converting enzyme inhibitor and angiotensin receptor blocker drugs of their benefits 'beyond blood pressure lowering' has been challenged on the basis of greater reduction in central and aortic pressure compared with brachial pressure measured by cuff sphygmomanometer, as shown by the pREterax in regression of Arterial Stiffness in a contrOlled double-bliNd study. Augmentation index is higher in hypertension, is inversely related to body height, and can be reduced by exercise. Augmentation index shows a linear relation with age up to 60 years. Regrettably, recent major trials such as the Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis, Prevention of Events with Angiotensin Converting Enzyme Inhibition, and Valsartan Antihypertensive Long-term Use Evaluation studies have not included pulse wave analysis to distinguish the relative benefit of different drugs.

Summary

Pulse wave analysis will assist in a better understanding of hypertension as well as in establishing the extent of cardiovascular disease and for monitoring therapy.

Keywords

arterial hemodynamics, blood pressure, hypertension, pulse wave analysis

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Abbreviations

ACEI	angiotensin-converting enzyme inhibitor
AIX	aortic augmentation index
ARB	angiotensin receptor blocker
CCB	calcium channel blocker
FDA	Food and Drug Administration
HOPE	Heart Outcomes Prevention Evaluation
PWV	pulse wave velocity
REASON	pREterax in regression of Arterial Stiffness in a contrOlled double-bliNd trial

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Introduction

The many advances in arterial hemodynamics that have occurred in recent years are set out in two books due for publication in 2005 – a fifth edition of McDonald's *Blood Flow in Arteries* [1••] and a multiauthored tome on arterial stiffness and wave reflection edited by Safar and O'Rourke [*2*••] in the Handbook of Hypertension series.

Rather than attempt to summarize the whole field in an article for clinicians, the course taken here is to concentrate on one aspect: pulse waveform analysis with arterial tonometry. This course embraces many of the new developments over the past year. We choose this approach because this new development can be used now by physicians to enhance their own practice. Recent authoritative articles in the United States [3•,4•], however, downplay this simple clinical approach while tending to emphasize sophisticated laboratory technologies.

Pulse wave analysis was used widely in European clinical practice in the late 19th century [5,6] but lapsed with introduction of the cuff sphygmomanometer [7]. The book by Postel-Vinay [7] is an underappreciated historical text, and even more relevant in the centennial year of Korotkov's publication. Waveform analysis was reintroduced after accurate arterial tonometers were developed by Millar and others, and were used to describe characteristic changes in the pulse waveforms with aging, disease, and vasoactive drugs [8–10]. The report by Kelly *et al.* [10] is a classic, with the key figure now in major textbooks. Progress in this field was interrupted by the premature death of tonometry's principal proponent [11] but has accelerated over the last year, principally in Europe.

Development of this field was summarized in the Folkow Lecture to the European Society of Hypertension in 2000 [12]. Application to stratification of risk in hypertension as evidence of target organ (large artery) damage was described in the European Society of Hypertension/European

Society of Cardiology guidelines [13], with emphasis on aortic pulse wave velocity as a measure of aortic stiffening, and on systolic augmentation of the central (carotid or aortic) pressure wave as a measure of the ill effect of such stiffening on the heart and central arteries. Such endorsement was not given in the US Joint National Committee 7 report, nor in the more recent American Heart Association reviews [3•,4•].

Arterial tonometry

The technique of arterial tonometry is increasingly used in clinical studies. The tonometer is similar to that used by ophthalmologists to record eyeball pressure. When applied gently over the radial or carotid artery so as to flatten the anterior wall, recordings of the pulse waveform are substantially similar to those recorded by a catheter within the artery [8]. Clinical emphasis has been on the radial pressure waveform since it is most easily recorded and on the carotid waveform (since it is similar to the aortic waveform). Femoral artery tonometry has been used only to measure delay in wave foot, and so to determine carotid-femoral pulse wave velocity as an index of aorta stiffening. Carotid tonometry is difficult, especially in persons with thick necks. It is uncomfortable for the patient, and its use carries a risk of carotid plaque dislodgement. Artefact is common, even in experienced hands, and is manifest as a wide range of values for time to the onset of the secondary systolic pressure wave and the amplitude of this wave [14,15].

Radial artery tonometry is easier to master, and variability is far less than in the carotid [16]. The report by Chen *et al.* [17] is the first and definitive article on tonometric frequency response and the use of transfer functions for pressure waveforms. An important advance in radial tonometry was the observation that pressure wave transmission in the upper limb is sufficiently constant under different conditions with age, disease, physiologic maneuvers such as Valsalva, and drug therapy for a generalized transfer function to be used to convert the radial to the aortic pressure wave [17] and thus to generate the aortic pressure wave from the radial waveform, calibrated to cuff pressures. This is used in one commercial device, SphygmoCor (AtCor Medical, Sydney, Australia, with which M.F.O. is associated) and gained US Food and Drug Administration (FDA) approval in 2001. The data on which approval was given were published during 2004 [18•,19•], but the validity of the technique is still debated, often on the basis of accuracy of the cuff sphygmomanometer to describe extremes (systolic and diastolic) of the brachial pressure pulse [4•]. Accuracy of the cuff sphygmomanometer is an entirely separate matter [20•,21] and an important issue in the interpretation of blood pressure measurements in all epidemiological studies and clinical trials. All assessment of transfer function presented to the FDA was undertaken with directly recorded arterial pressure values as the 'gold standard' [18•,19•].

This issue has not been settled completely, but at this time, there is more general (as well as FDA) acceptance of the value of a generalized transfer function for generating central from upper limb pressure waveforms.

Another commercial device, Jentow, has been developed by the Colin Medical Technology (Komaki, Japan) company and concentrates on features of the radial waveform as recorded by an array of tonometers [22–24]. Omron Healthcare (Kyoto, Japan) also has developed a machine to record radial artery pressure using the tonometric method [25], and radial augmentation index is calculated automatically using a fourth-order differential equation [26].

Peripheral systolic, diastolic, mean and pulse pressure and cardiovascular events

Recent studies confirm the landmark Systolic Hypertension in the Elderly Program (SHEP) study [27] in identifying systolic pressure as of greater prognostic importance than diastolic pressure for cardiovascular events, at least in persons over 50 years. SHEP was an important study showing the greater importance of systolic than diastolic pressure for predicting cardiovascular events in elderly persons. Contrary evidence in the older trials can be explained on the basis of greater amplification of the pressure wave in the upper limb of young persons [28]. Attention is now directed at pulse pressure, and a series of studies has shown the greater importance of pulse pressure over diastolic, systolic, and mean brachial pressure, at least with respect to cardiac ischemic events [29•,30•,31,32••]. The data challenge the Blood Pressure Lowering Treatment Trialists' Collaboration [33], which showed no association between pulse pressure and cardiovascular events. The most recent studies show greater value for calculating 24-hour pulse pressure in predicting cardiovascular events [34,35].

Central systolic, diastolic, augmented, mean and pulse pressure and cardiovascular events

Diastolic and mean pressure are virtually identical in central and peripheral arteries [19••], so that differences relate only to systolic, augmented, and pulse pressure values. A series of studies have been concluded with central systolic, pulse, and augmented pressure measured either directly at diagnostic catheterization or indirectly from the transfer function or other techniques. Despite relatively small numbers, these have shown, uniformly, a relation with cardiovascular events and with outcomes [36••–38•,39,40••] (Table 1). These studies were not sufficiently large to show such a relation for peripheral pressure values. Some of the studies were directed to augmentation index, the ratio of the central augmented

Table 1. Summary of publication with small numbers (40–1337 persons), showing relationship between central (aortic or carotid) pressure and cardiovascular disease

Measure of aortic/carotid pressure	Author	Country	Measure of outcome
Pulse pressure invasive	Lu *et al.*	China	Restenosis after coronary angioplasty
	Nishijima *et al.*	Japan	Severity of coronary disease
	Chemla *et al.*	France	Relation to concentric LV hypertrophy
	Philippe *et al.*	France	Extent of coronary disease
	Nakayama *et al.*	Japan	Restenosis after coronary angioplasty
	Danchin *et al.*	France	Presence and extent of coronary disease
	Jankowski *et al.*	Poland	Extent of coronary disease
Pulse pressure non-invasive	Waddell *et al.*	Australia	Predictor of coronary atherosclerosis
	Safar *et al.*	France	All cause and cardiovascular mortality
	Boutouyrie *et al.*	France	Carotid intima-media thickness
	Boutouyrie *et al.*	France	Regression of carotid intima-media thickness with change in carotid pulse pressure
	Boutouyrie *et al.*	France	Primary coronary events
	Jondeau *et al.*	France	Aortic dilation in Marfan's syndrome
Augmentation Index invasive	Hayashi *et al.*	Japan	Severity of coronary disease
	Ueda *et al.*	Japan	Restenosis after coronary angioplasty
	Chirinos *et al.*	USA	Major adverse cardiovascular events
Augmentation Index non-invasive	London *et al.*	France	All cause and cardiovascular mortality
	Saba *et al.*	Italy	LV hypertrophy, carotid remodelling
	Weber *et al.*	Austria	Extent and severity of coronary disease
	Nurnberger *et al.*	Germany	Cardiovascular risk
	Weber *et al.*	Austria	Major cardiovascular events
	Weber *et al.*	Austria	Diastolic dysfunction
Fractional systolic/diastolic pressure	Jankowski *et al.*	Poland	Extent of coronary disease
	Nakayama *et al.*	Japan	Risk of coronary disease
	Nishijima *et al.*	Japan	Risk of coronary disease
Fractional pulse pressure, pulsatility index	Jankowski *et al.*	Poland	Extent of coronary disease
Systolic pressure	De Luca *et al.*	Europe/Australia	Regression of LV hypertrophy
Ejection time	Weber *et al.*	Austria	Diastolic dysfunction

LV, left ventricular. After O'Rourke MF. Am J Hypertens 2004; 17:721–723.

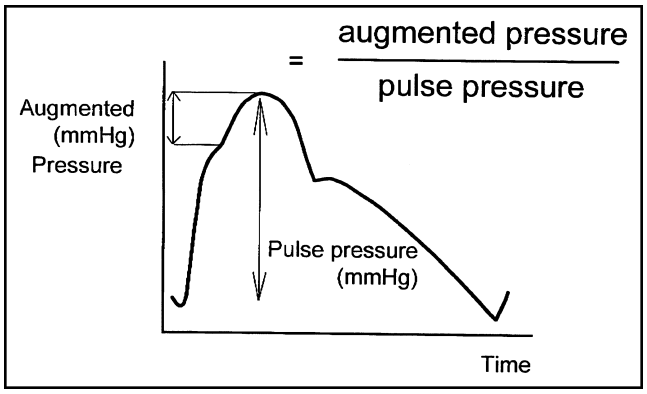
pressure wave to the central pulse pressure (Fig. 1). This ratio overcomes one of the major problems already noted in this area, of cuff pressure inaccuracy [1••,4•], since it relates one component of the pressure wave to another component. All published studies of augmentation index show a positive relation to cardiovascular events and to outcomes. They thus confirm the life insurance studies of a century back in which persons with high augmentation of the (radial) pressure wave were rejected on the basis of 'anticipated arterial senility' [7].

Arising from this work is the concept of arterial age as calculated from the augmentation index of a patient (adjusted to heart rate) compared with population normals. Chronological age dominates all other risk factors in calculation of cardiovascular risk. Use of 'arterial age' determined from tonometry or other methods may provide a benefit in determination of cardiovascular risk from standard tables. This concept of 'arterial age' [1••] has not yet been tested. Augmentation index is discussed separately in this report.

Central systolic, augmented, and pulse pressure in drug studies

The most recent report of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study [41] raises again the issue of supposed benefits of specific angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) drugs 'beyond blood pressure lowering' and concluded 'losartan has direct cardiac benefits.' This conclusion has been challenged [42], as was the original claim made for the Heart Outcomes Prevention Evaluation (HOPE) study [43,44], on the basis that arterial dilating drugs such as nitrates, calcium channel blockers (CCBs), ACEIs, and ARBs reduce left ventricular and aortic systolic pressure to a greater degree than measured in the upper limb. This result was originally shown in the invasive studies of Kelly *et al.* [10], then confirmed repeatedly in invasive and noninvasive studies that have used carotid and radial tonometry with or without

Figure 1. Augmentation index (%)



application of a generalized transfer function [1••]. The most recent blinded comparison of atenolol against ramipril [45] showed that for identical reduction in diastolic pressure, central systolic and pulse pressure were reduced by 5 mmHg more than measured in the brachial artery. Such a fall in the HOPE study could readily explain the beneficial effects of ramipril and raised the question whether benefits were 'beyond blood pressure' or 'beyond the brachial artery.' HOPE, LIFE, and other major trials have not included arterial tonometry, but the pREterax in regression of Arterial Stiffness in a contrOlled double-bliNd (REASON) study [46•], which compared a perindopril-indapamide combination against atenolol, showed an estimated 12 mmHg greater fall of pressure in the aorta with the combination than measured by cuff. This was associated with a greater fall in left ventricular mass in patients receiving perindopril-indapamide than those receiving atenolol [47•].

The issue of differential reduction in aortic compared with brachial pressure is systematically ignored in recent major clinical trials. These trials were designed on the premise that the 19th century cuff sphygmomanometer provides an accurate measure of left ventricular load and needs no supplement from other methods. Its is ironic that the introductory section of at least one major cardiology textbook highlights this issue [48•], while designers of clinical trials and editors and reviewers of major journals cast a blind eye. Yet, as in REASON, the methods used are readily applied in office practice – and indeed were so applied and published by practitioners in general practice over 100 years ago [1••,5–7].

An exception is the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study, which has just been concluded and which included a substudy on arterial tonometry [49]. Initial results of this study were presented to the American College of Cardiology Annual Scientific Meeting in 2005.

Aortic augmentation index

Aortic augmentation index (AIX) is a measure of the ill effect of arterial stiffening, since it relates pressure augmentation, caused by early wave reflection, to total pulse pressure in the aorta. Aortic AIX is consistently higher than AIX in the radial artery [50•], and both increase progressively with age [1••,50•]. Aortic AIX is consistently higher in women than in men [50•], a difference associated with higher aortic pulse pressure in women [51•], and may be an important factor in the high prevalence of left ventricular hypertrophy [52•], diastolic left ventricular dysfunction [53], and cardiac failure in older women [1••], and myocardial ischemia with lesser degree of coronary stenosis in women [54•].

Aortic augmentation index is higher in normotensive offspring of families with essential hypertension [55•] and is associated with genetic polymorphism [50•,56•]. AIX is increased in patients with sickle cell disease [57•] and in patients with high C-reactive protein [58•–60•]. It is increased in hypertensive pregnancy [61•]. It is related inversely to body height [1••,50•,62•], which may largely explain gender differences and the favorable effect of tall stature on cardiovascular outcome in men [51•]. In the HOORN study (Hoorn, Nederland), AIX was related to body fat composition, as were other indices of arterial stiffness [63•].

Aortic augmentation index can be reduced by exercise [64•,65•], with the effect coming on within 3 months and wearing off within 1 month. Such a beneficial effect of exercise training can be attributed to improved endothelial function of muscular arteries, with relative dilation and so reduction in peripheral wave reflection [66]. AIX is increased with smoking and with caffeine ingestion – with the two combined exerting a synergistic detrimental effect on central pressure and left ventricular load [67•]. AIX is reduced with vasodilator therapy [68•], as discussed.

Augmentation index and pulse wave velocity

Estimation of carotid AIX and aortic pulse wave velocity (PWV) have been incorporated in the Framingham study, and preliminary results have been published [69•]. Aortic PWV was shown to increase progressively and apparently in a linear fashion with age, while (also in conformity with other studies [1••]) brachial PWV remained constant through adult life. In this study, however, AIX appeared to decrease with age in older women [69]. This finding has been challenged, as have other interpretations from Framingham [70,71]. No doubt exists at all that AIX shows a curvilinear relation with age, tending to flatten out over age 60 years. This result [1••,72] has been attributed to change in shape of the aortic flow waveform with development of left ventricular hypertrophy and increased duration of ejection. With the development of systolic heart failure, change in the pattern of ventricular ejection and decrease in the ejection duration can cause further reduction in AIX. As an index of aortic stiffness, AIX is useful only when ventricular ejection is normal, when peripheral wave reflection is normal, and when factors with alter ejection duration (such as heart rate) are controlled.

Major trials on different classes of blood pressure lowering drugs

The results of major trials have been reported in recent journals [73•–75•]. In the Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study for normotensive patients with coronary disease, while both amlodipine and enalapril reduced brachial cuff blood pressure to a similar degree, the CCB significantly reduced cardiovascular events, but there was less benefit for the ACEI [73•]. In the Valsartan

Antihypertensive Long-term Use Evaluation (VALUE) trial, there was no difference between the two drugs in cardiac mortality and morbidity [74•] but greater early reduction in brachial cuff pressure with amlodipine. While the HOPE study claimed that the ACEI ramipril effectively reduced cardiovascular mortality and morbidity through a 'benefit beyond blood pressure lowering,' the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) study [75•] found that the addition of ACEI over standard therapy in patients with stable coronary disease did not provide further benefit. The conclusion from these studies is that beneficial effects cannot always be judged from conventional cuff recordings [76,77].

The most recent published meta-analysis showed minor benefit between different drug classes other than reducing blood pressure [78,79••]. These beneficial effects can perhaps be explained on the basis of central systolic and pulse pressure lowering. Further analysis showed that if reduction in central systolic pressure was taken into account (calculated about 3 mmHg lower than brachial pressure with arterial dilators), there was an almost linear inverse relation with the risk of stroke [1••]. This is supported by Hirata *et al.* [45], who showed a 5.2-mmHg decrease in central systolic, augmented, and pulse pressure with ACEI (ramipril 10 mg) compared with β-blocker (atenolol 100 mg).

Conclusion

Pulse wave analysis with arterial tonometry will be used more widely in the future to establish the extent of cardiovascular disease and to monitor drug therapy, and as an easy approach for better understanding of hypertension. If only recent major trials had included the use of pulse wave analysis to measure central hemodynamics, there might be a clearer conception on relative benefit of different drugs. This was partially achieved in REASON [46•,47•] and will be examined in the forthcoming Anglo-Scandinavian Cardiac Outcomes Trial [49].

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