Pulse wave analysis and pulse wave velocity: a critical review of their strengths and weaknesses

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The study of the pulse using the technique of applanation tonometry is undergoing a resurgence with the development of new computerized equipment. We aim here to present a critical review of the uses, potential uses, strengths and weaknesses of the technique of applanation tonometry for the assessment of augmentation index and pulse wave velocity. We will review the technique of applanation tonometry, the physiological factors affecting pulse wave velocity and pulse wave analysis, the changes in pulse wave velocity and pulse wave analysis with pharmacological interventions, and the use of the technique of applanation tonometry as a prognostic tool. We conclude that, although the technique of applanation tonometry initially seems promising, several pertinent issues need to be addressed before it can be used reliably as a clinical or research tool. Importantly, use of the technique of applanation tonometry to derive the central waveform from non-invasively acquired peripheral data needs to be validated prospectively. *J Hypertens* 21: 463–472 © 2003 Lippincott Williams & Wilkins.

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Introduction

The sphygmograph has been used for the study of the pulse pressure wave since the late 1800s, when clinicians such as Osler and Mohamed relied heavily upon it in the course of clinical diagnosis [1]. Nevertheless, it was superseded at the turn of the last century, when the sphygmomanometer was invented for blood pressure reading. Since that time, blood pressure recording has become more and more widely used for clinical purposes, culminating in large trials – for example the Framingham study, which has clearly demonstrated the link between blood pressure and cardiovascular disease [2]. The Framingham study also demonstrated the link between hypertension and left ventricular mass (LVM), showing that for each 20 mmHg increase in blood pressure there was an associated 10.6 g increase in LVM. The association between LVM and adverse outcome is well known [3].

Despite the results of the Framingham study, measurement of blood pressure in the brachial artery still attracts criticism, a common reason being that the brachial artery is not subject to the adverse, atherosclerotic effects of hypertension. However, the main reason for the criticism is that the left ventricle is likely to be influenced directly, not by the pressure in the brachial artery, but by the pressure in the ascending aorta [4,5].

Recently, with the development of new computerized equipment, assessment of the pulse pressure wave with a sphymograph is undergoing a renaissance. Technology has progressed since the days of Osler and Mohamed, and computer software now allows estimation of the ascending aortic pressure wave from that assessed peripherally, in the radial artery. Many of the proponents of the sphygmograph are encouraging its use on the basis that it gives a better indication of the blood pressure that directly affects the heart (i.e. that in the ascending aorta) than does simple peripheral blood pressure measurements. The simplicity of the sphymographic technique of assessing the peripheral pulse waves and the portability of the equipment are obvious advantages for the use of the sphymograph as a research tool in clinical and epidemiological trials. It may also become established as a powerful clinical tool if it proves its worth in longitudinal studies. We aim in this review to discuss briefly the method of pulse wave analysis (PWA) to derive the central aortic pressure waveform, and the method of calculating pulse wave velocity (PWV) using applanation tonometry. We will then assess the evidence currently available to help us to decide whether these methods can add anything to blood pressure measurement as a tool for assessing and treating disease.

There are many methods of assessing the pulse wave. It is possible to record the volume waveform of the pulse, for example with photoplethysmography [6], or the pressure wave may be assessed by means of applanation tonometry. There are two main methods of using applanation tonometry to assess the pulse pres-

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sure waveform. It can be analysed by applying a valid transfer function based on Fourier analysis, which allows derivation of an aortic pressure waveform, the augmentation index and time to reflected wave [7–9]. The pulse pressure wave can also be analysed using a modified Windkessel model of the circulation, which allows calculation of large- and small-vessel compliance [10]. We will limit this review to the assessment of the pulse pressure wave by the technique of applanation tonometry using the method based on Fourier analysis; a thorough review of all the methods of assessing the pulse wave is beyond the scope of this article. We will also review the applications of the assessment of PWV.

Methodology of pulse wave analysis

The pulse, rather than being a unit of pressure the limits of which are defined by the upper and lower limits of blood pressure, is actually a series of harmonics travelling along the arterial tree, rather as on a plucked violin string. It can be described in terms of pressure, flow and dimension. The pulse pressure wave is formed from the combination of the incident wave (i.e. the pressure wave generated by the left ventricle in systole) and waves reflected back from the periphery [5]. The technique of applanation tonometry detects this pulse pressure wave by using a micromanometer-tipped probe. The artery is compressed between the sensor and the underlying structures, and thus the intra-arterial pulse pressure is transmitted through the arterial wall to the sensor. This pressure waveform is then digitalized such that it can be viewed on a computer screen.

The pulse pressure waveform

The pulse pressure waveform varies in different vessels in the same individual, and is dependent on:

- the viscoelastic properties of the artery (which cause amplification of the wave as it travels from more elastic central to stiffer peripheral arteries)
- the viscosity of the blood
- wave reflection
- wave dispersion.

Current computer software goes one step further than purely looking at the peripheral waveform and now allows calculation of the central aortic pressure and waveform from the radial or carotid pulse pressure waveform, calibrated using peripheral blood pressure. This requires the use of a mathematical equation, the 'generalized transfer function' that can be built into the computer software. Many transfer functions exist [7,11,12] and have been derived as a result of studies recording the peripheral waveform at the same time as the central ascending aortic waveform obtained invasively.

Augmentation of the pulse pressure waveform

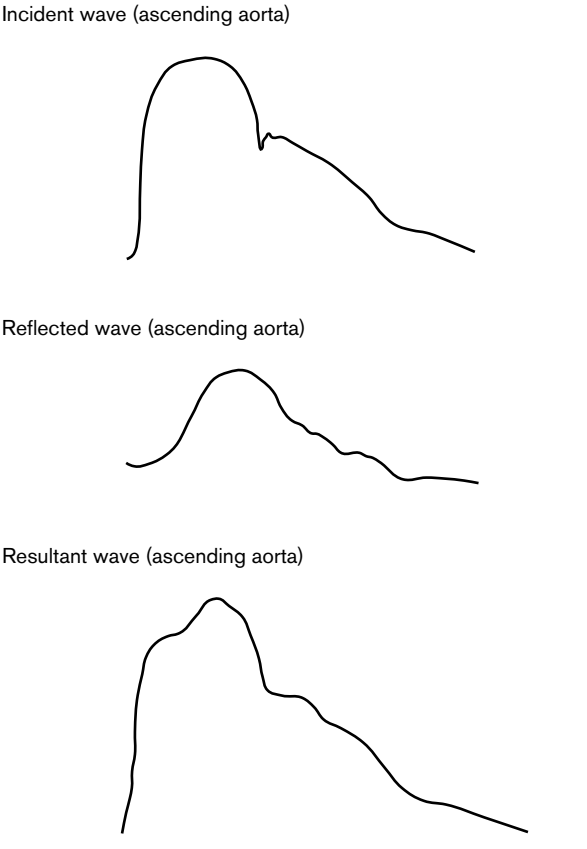
Wave reflection leads to augmentation of the aortic pressure wave. As the incident wave travels from the left ventricle to the periphery, it reaches vessels of greater impedance that act as a mirror, reflecting it back to the aorta. Thus the resulting pressure in the ascending aorta is the sum of the incident and reflected wave (Fig. 1).

Augmentation index

The augmentation index is a measure of the effect of wave reflection on the second systolic peak and thus is one measure of the additional load to which the left ventricle is subject as a result of wave reflection. It is calculated as the increment in pressure from the first shoulder in the ascending aortic pressure wave to the peak of this wave expressed as a percentage of the peak ascending aortic pressure wave (Fig. 2). It depends on:

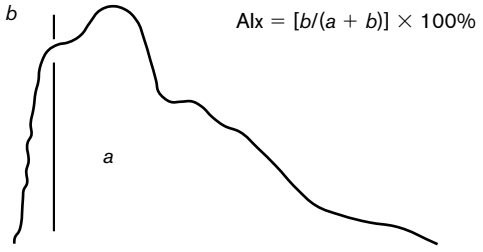
- the duration of the cardiac cycle (which depends on the heart rate)

Fig. 1



Incident and reflected waves combine to produce the observed pressure waveform (these waveforms are not actual).

Fig. 2



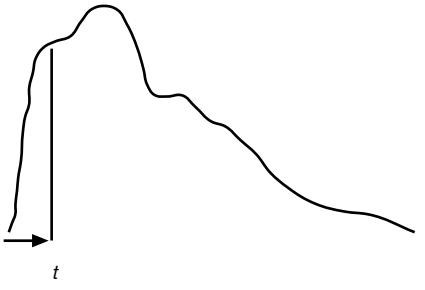
Calculation of augmentation index (AIx).

- the speed of the pulse wave
- the amplitude of the reflected pulse wave.

For a given heart rate, the time of arrival of the reflected wave (Fig. 3 depends on the PWV, which is determined by the stiffness of the vasculature (PWV increases with increasing vessel stiffness). If the reflected wave arrives early in the cardiac cycle it combines with the incident wave giving a greater ascending aortic pressure against which the left ventricle has to pump; however, if it arrives later in the cardiac cycle it increases the ascending aortic pressure in diastole, leading to improved coronary circulation.

The fact that PWV is dependent on arterial stiffness is one of the reasons that the augmentation index, which has been correlated with PWV [13], has been proposed as a marker for arterial stiffness [14,15]. However, the relationship between PWV and the augmentation index may not be as clear cut as initially believed. Kelly *et al.* [16] found that the augmentation index was correlated with PWV, age and blood pressure in univariate analysis; however, in multivariate analysis it was related only to age. The investigators suggested that the relationship between the augmentation index and PWV may be stronger when the aorta becomes stiffer, as PWV may not change greatly whilst the aorta remains elastic. Thus, in an elastic aorta, the augmentation index is more likely to be related to the intensity of the reflected wave rather than to its velocity. The theory proposed by Kelly *et al.* [16] is supported by the observation that angiotensin II (Ang II) and glyceryl trinitrate (GTN) had a marked effect on the augmentation index, whilst only having a small effect on PWV. This result could be explained by Ang II and GTN changing the intensity of the reflected wave form, whereas any change in PWV is absorbed by the elasticity of the aorta. It is, however, worthy of note that many authors have studied PWV only in the aorta, even though, in terms of wave reflection and vascular stiffness, the important measurement is PWV along the *entire* arterial tree. Also, even small changes in PWV may be important: Guerin *et al.* [17] found that the adjusted relative risk for all-cause mortality for a decrease in PWV of 1 m/s was 0.71 (95% confidence interval 0.6 to 0.86); many small studies will have lacked the power to detect such a small change in PWV.

Fig. 3



Time to reflected wave (*t*).

Pulse wave velocity

$$\text{Velocity} = \text{distance}/\text{time}$$

To calculate the PWV, the time delay between the pulse pressure wave at two different sites a known difference apart has to be calculated. This can be done either by placing a probe on each site (usually the carotid and radial, or carotid and femoral) and recording the waveforms simultaneously, or by recording the waveforms at the different sites independently but comparing the time delay at both sites against a simultaneously measured QRS complex.

The theory is simple: all that is needed is to divide the distance between the two sites at which the pressure wave is being recorded, by the time taken from the first to the second site. Time is calculated from the foot of the pressure wave at the first point to the foot of the pressure wave as it arrives at the next point. However, difficulties are encountered in judging accurately where the foot of the wave is. For example, is it at the point of minimal diastolic pressure, or is it at the point at which the first derivative of pressure is at a maximum? There are currently four different methods for calculating the location of foot of the wave. However, the method using the point at which the second derivative of the pressure wave is maximal (second derivative method) and the method looking at the point yielded by the intersection of a line tangent to the initial systolic upstroke of the pressure tracing and a horizontal line through the minimal point (intersecting tangent method) are the most reproducible [18].

Are the techniques of PWA and PWV reproducible?

There are small differences in reproducibility between the different systems that can be used, but in general the technique of applanation tonometry is simple to learn, and once it has been learnt there is good inter- and intra-operator reproducibility [19]. Good repeatability of measurements performed on two separate occasions has been reported [20]. It is a matter for concern, however, that Chiu *et al.* [18] have reported a variation of up to 16% in PWV between separate study days; if this were consistently found to be the case, the use of PWV would be limited to the study of interventions that are expected to produce a large magnitude of response. Chiu and colleagues suggested that this longitudinal variation could be due to changes in blood pressure, respiratory changes in arterial pressure, or movement of the transducer on the skin overlying the arteries. Published guidelines do exist to help to standardize measurement conditions and hence reduce longitudinal variation in PWV measurement [21].

It is also important to mention here that different studies have not always used the same sites for the assessment of PWV: whereas some authors have used carotid–radial PWV, others have used carotid–femoral PWV. The difference in elasticity and propensity to atherosclerosis of the particular arterial system studied may well be the cause of the incompatibility between results when studies are compared.

Has the technique been validated?

Pulse wave analysis (assessment of the augmentation index)

The transfer functions used in commercially available software packages for the assessment of the augmentation index are based on those derived from studies in patients undergoing cardiac catheterization. These various transfer functions have given similar results when applied to data acquired in subsequent studies, which supports their reproducibility and applicability [7,11]. Nevertheless, there are concerns regarding the use of applanation tonometry to derive the central aortic pressure and the augmentation index. The main concern is that the technique of superficial applanation tonometry has not been tested prospectively [22,23].

There have been many studies performed that have aimed to validate the transfer functions. Chen *et al.* [24] studied patients undergoing diagnostic cardiac catheterization, and using their own transfer function found a good correlation between augmentation index assessed using applanation tonometry at the carotid artery and that assessed centrally and invasively. Other investigators have looked at the estimation of the aortic pressure waveform using applanation tonometry at the radial artery; again, they found good correlation between the invasive and non-invasive methods [11,25]. Unfortunately, in general the transfer function used by Chen *et al.* [11] underestimated the non-invasive measure of the augmentation index when compared with that obtained invasively. A weakness in the interpretation of the results of these studies is that, in all of them, acquisition of peripheral pulse waveforms or blood pressure readings used to calibrate the waveforms, or both, were obtained invasively.

In another study [12], Chen's group attempted to test prospectively their own system for calculating central aortic pressure and augmentation from radial artery tonometry, but found, in the majority of patients, that the estimated aortic pressures varied by more than 10% from the simultaneously acquired invasive data when the radial pressure waves were calibrated using the peripheral blood pressure. Hence, they also used invasively measured intra-aortic blood pressure for calibration of the radial pulse wave.

Thus, although the transfer function itself seems to be accurate, it seems that inaccuracies are incurred when calibrating the peripheral waveforms. Obviously, it makes no sense to use PWA if the radial artery waveforms have to be calibrated using invasively obtained intra-aortic blood pressure for accuracy.

Given that mean arterial pressure (MAP) does not vary within the arterial system, it should be possible to achieve accurate calibration of the radial pressure waveform using brachial artery measurements. However, there has been as yet only one reported study that compared intra-arterial measurements with those using applanation tonometry at the radial artery. This study revealed a mean difference between the invasive and estimated measures of 11 mmHg for systolic and 8 mmHg for diastolic blood pressure [26].

Thus, although the transfer function theory is attractive conceptually, we lack proper confirmation, in a prospective study, that PWA performed and calibrated entirely non-invasively, at peripheral sites, does accurately reflect central aortic pressure.

Pulse wave velocity

The assumptions used in performing PWA do not apply to the assessment of PWV.

We know of no human studies comparing invasively measured PWV with that obtained non-invasively using applanation tonometry; however, PWV assessed using transcutaneous photoplethysmography does correlate well with PWV values obtained invasively [27].

It should be noted that non-invasive data suffer more

noise and drift than do data obtained invasively, which may lead to inaccurate results [18].

Physiological factors affecting PWA and PWV

Heart rate

It is well known that the augmentation index changes with acute changes in heart rate. Wilkinson *et al.* [28] demonstrated this very elegantly in patients undergoing diagnostic cardiac catheterization; all had normal left ventricular function. Increasing heart rate using right atrial pacing was accompanied by a linear decrease in the augmentation index of 5.6% for each 10 beats/min increase in heart rate. There was no effect of heart rate on recorded systolic, diastolic or mean blood pressure, or on peripheral pulse pressure. A similar effect has also been seen in older individuals [29]. This inverse relationship between heart rate and the augmentation index is explained by the fast heart rate, which decreases the duration of ejection, with the result that the reflected wave arrives later in the cardiac cycle relative to the incident wave; this phenomenon is not a result of the reflected wave returning earlier. Therefore, with faster heart rates, the reflected wave is more likely to arrive in diastole and thus the left ventricle has to work against a smaller pressure, and there is greater perfusion to the coronary arteries (which occurs in diastole) [5]. This concept is, however, contrary to our general belief that a slower heart rate is better prognostically. In addition, β-blockers, which slow the heart rate and therefore increase the augmentation index, have also been shown to have great prognostic benefit in the treatment of heart failure and, to a lesser extent, in hypertension. Heart rate also affects amplification of the pulse pressure wave such that amplification is less with slower heart rates.

The relationship between PWV and heart rate is a little less clear. Some cross-sectional studies have shown no association between the two [13,30], but others have indicated that PWV does vary with heart rate [31,32]. Studies using pacing to alter heart rate have also yielded conflicting results. Wilkinson *et al.* [28] found no change in PWV with increasing heart rate, but Lantelme *et al.* [33] found that PWV was significantly increased by increasing heart rate. Therefore, at present, caution must be exercised when results are interpreted from both PWA and PWV if interventions that alter heart rate are being used.

Height

An inverse relationship exists between the augmentation index and body height [13,16]. This is assumed to be due to the shorter distance from the origin of the waveform to the point of reflection, leading to a quicker return of the reflected wave for a given PWV, and is often given as an explanation for the increased augmentation index seen in women. It is therefore interesting that Yasmin and Brown [13], although confirming the relationship between height and the augmentation index, found this to be less robust when the sexes were analysed separately. This may well be due to a reduction in power when the group was split into different sexes, but it does agree with the findings of an earlier study [34], and it may be that height is a surrogate for other differences between the sexes.

It has been suggested that height should be controlled for in the analysis of results. Conversely, it may be that the increase in augmentation seen in shorter people contributes to the genuine increase in cardiovascular risk seen with decreasing height [35,36], and this increase in the augmentation index may be contributing to the excess cardiovascular risk even when systolic blood pressure is normal. This excess risk may be attributable to the effect of height itself causing an increase in the augmentation index [36], or may result from the association of short stature with other known risks for cardiovascular disease, for example decreased forced expiratory volume and peak expiratory flow [37].

Ageing

It is well known that arteries become less elastic as people age. This is caused by an increase in arterial wall thickness secondary to hyperplasia of the intima and also by loss of elastin in the media and its replacement with collagen. These changes in the vasculature associated with ageing are reflected in an increase in the augmentation index and PWV, and also an increase in brachial blood pressure and MAP [38]. However, in one study the augmentation index and PWV were increased out of proportion with the age-related increase in blood pressure, suggesting that ageing-related changes in the vasculature may be underestimated by assessment of blood pressure [38]. The same investigators also found oxygen consumption as assessed by maximum oxygen consumption (VO_{2max}) to be related to PWV, systolic blood pressure and the augmentation index, even when age was controlled for. This suggests that increasing arterial stiffness may contribute to lower VO_{2max}, possibly by decreasing muscle blood supply, although it may be more likely that differences in lifestyle factors consecutively lead to both an increase in the augmentation index and a decrease in VO_{2max}.

Decreased pulse pressure wave amplification is also seen with ageing [39], such that, whereas in younger people peripheral systolic blood pressure overestimates central systolic blood pressure [40], in older people these values are similar [5]. This may be why systolic blood pressure is a better predictor of cardiovascular risk in older people, whereas diastolic blood pressure is a better predictor in younger people.

Cross-sectional studies

Are risk factors for cardiovascular disease and atherosclerotic load associated with increased PWV and the augmentation index? If so, this would bolster the case for using PWV/the augmentation index as useful markers of atherosclerotic risk. However, it would not exclude the possibility that the same processes leading to atherosclerosis are causing increased arterial stiffness.

Arterial stiffness assessed by a variety of methods has been correlated with insulin, cholesterol and triglyceride concentrations [41,42], and PWV correlates to the number of (treated and non-treated) cardiovascular risk factors, atherosclerotic events and cardiovascular risk as predicted by the Framingham risk equations [43,44]. PWV is also positively correlated with carotid intima–media thickness – not only a marker of atherosclerotic burden in the carotid artery, but also a reflection of that in the coronary arteries [45,46]. Both intima–media thickness and PWV increase with risk factors for cardiovascular disease.

It is of interest here that, in a population of patients with type 2 (non-insulin-dependent) diabetes mellitus, increased arterial stiffness (assessed invasively in the brachial artery) was apparent before any clinical manifestations of cardiovascular disease [47], and that healthy offspring of patients with type 2 diabetes have also been shown to have an increased PWV [48,49]. This evidence certainly lends weight to the thesis that blood vessel dysfunction may precede the development of diabetes [50], and it may also be that vascular stiffness precedes atherosclerosis and is a risk factor for atherosclerosis. However, as yet there have not been any longitudinal studies assessing the long-term consequences of vascular stiffness on prognosis in diabetes.

PWV is increased in both type 1 (insulin-dependent) and type 2 diabetes, but the evidence is more uncertain in relation to the augmentation index. Some authors have found that the index is indeed increased in diabetes, but O'Brien *et al.* [51] found, after controlling for heart rate, no increase in the augmentation index in a large number of diabetic patients. However, the use of different systems to assess the augmentation index in patients with diabetes may be a reason for the heterogeneity of results [47,52,53].

These studies clearly demonstrate that PWV and the augmentation index are associated with the structural changes of atherosclerosis.

Left ventricular mass index

Increased LVM is well known to be a poor prognostic marker, thus indices that are strongly and positively associated with increasing LVM index (LVMI) are also likely to confer a similarly poor prognosis. It would be logical that LVM would be affected to a great extent by the pressure in the ascending aorta; indeed a greater estimated augmentation index is associated with a greater LVMI [46]. Given that the augmentation index is in part determined by PWV, it is puzzling that Chen *et al.* [54] found that LVMI was correlated to PWV only in a univariate analysis, whereas in multivariate analysis the effect of PWV on LVMI could be accounted for by the effect of blood pressure. It may be that the augmentation index gives a better reflection of systemic vascular stiffness than PWV because the augmentation index is affected by the amplitude of the reflected wave in addition to its velocity. Furthermore the aorta, being an elastic artery, may well not manifest the effects of atherosclerosis until later in the disease process. It is also worthy of note that, in their study, Saba *et al.* [46] did not control for the effect of heart rate on the augmentation index, which may have biased the results in favour of the augmentation index as a predictor of LVM.

Changes in PWA and PWV parameters with interventions

The next issue is whether treatment-induced changes in the augmentation index and PWV are accurate surrogates for whether that particular treatment will reduce adverse cardiovascular effects. If the augmentation index and PWV are found to change for the better with beneficial interventions and for the worse with interventions that are harmful, this would help to support the case being made for their being useful clinical measures.

Angiotensin II

Angiotensin II is known to contribute to vascular remodelling and therefore its expected effect would be to increase PWV and the augmentation index. In fact, acutely, Ang II has been shown to increase the augmentation index independent of PWV and heart rate [16], suggesting that its effects on the augmentation index may be due to effects on the tone of small arteries near the sites of wave reflection, creating a greater intensity of wave reflection. Ang II also increases PWV, but this effect is not as marked as the increase in the augmentation index, and it may be that prolonged exposure to Ang II is necessary to increase vessel stiffness and PWV. The fact that PWV was not greatly affected despite large alterations in blood pressure suggests that increased PWV is likely to be associated with hypertension only when structural alterations have occurred.

L-N^G-Monomethyl arginine

Nitric oxide is formed by the action of nitric oxide synthase on L-arginine; L-N^G-monomethyl arginine (L-NMMA) is an L-arginine analogue that inhibits nitric oxide synthase. Nitric oxide has beneficial effects on

the blood vessels: it acutely causes smooth muscle relaxation and chronically regulates vascular growth by inhibiting smooth muscle cell proliferation and migration [55]. Thus PWV and the augmentation index as measures of vascular stiffness would be expected to increase with nitric oxide inhibition.

Indeed, although there are no data regarding PWV as assessed by applanation tonometry, invasively recorded brachial artery PWV does increase after L-NMMA infusion, suggesting that acute inhibition of nitric oxide release leads to adverse effects on vascular stiffness [56]. The augmentation index has also been demonstrated to be increased after L-NMMA infusion [57], although this increase can be partly, but not entirely, explained by an associated decrease in heart rate. The increase in the augmentation index secondary to L-NMMA is accompanied by an increase in estimated central pulse pressure, but not measured peripheral pulse pressure, suggesting that nitric oxide inhibition with L-NMMA may have more effects on central than on peripheral blood pressure.

Reports of the effects of L-NMMA on vascular stiffness do not agree in all the published literature [58]; however, many studies have demonstrated that changes in peripheral (brachial) blood pressure measurements do not always reflect estimated ascending aortic blood pressure when substances such as noradrenaline, Ang II, caffeine and L-NMMA are given [16,57,59,60]. If the estimated readings for ascending aortic pressure are correct and ascending aortic pressure is indeed found to be important with respect to cardiovascular disease, we may find that we are losing much valuable information by recording only brachial blood pressure.

Angiotensin-converting enzyme inhibition

Angiotensin-converting enzyme (ACE) inhibitors are known to decrease cardiovascular mortality [61] as a result of their many beneficial vascular effects, and thus could be expected to improve PWV and the augmentation index.

Angiotensin-converting enzyme inhibition with benazepril certainly increases measurements of radial artery compliance in patients with heart failure when assessed by an echo-tracking device [62], and ACE inhibitors also reduce the augmentation index and PWV assessed by applanation tonometry in patients with hypertension [63,64].

It has been suggested that the reduction in LVM seen with ACE inhibition may be related to the decrease in PWV, but it is not known if the reduction in LVM is a result of the reduction in PWV. If this were the case, this would lend further weight to the argument that indices of vascular stiffness are useful for gauging cardiovascular risk.

β-Blockade

β-Blockers have been shown to improve morbidity and mortality outcomes in patients with heart failure [65–67] and reduce LVM in those with hypertension [68]. Stimulating the sympathetic nervous system with noradrenaline results in an increase in MAP, PWV and the augmentation index, which would be consistent with noradrenaline exerting adverse effects on the vascular system [60], and some β-blockers (e.g. bisoprolol) do improve vascular stiffness as demonstrated by a decrease in PWV [69]. Unfortunately, this short-term effect on PWV has not been shown to be maintained in the long term [70].

It may well be found that different types of β-blocker have different effects on vascular stiffness as a result of dissimilar receptor affinities. For example, some β-blockers lead to an increase in augmentation index by decreasing heart rate, whereas other β-blockers that have vasodilating properties lead to a decrease in the augmentation index [71]. β-Blockers also prolong diastole, thus the increase in the augmentation index seen with some of these agents may be offset by a beneficial effect on coronary artery perfusion.

The data so far with respect to β-blockers may suggest that the augmentation index and PWV are relatively unimportant measures of outcome response, which is possible because the benefit seen with β-blockers may relate to their myocardial protective actions rather than to their vascular effects. However, it may be that selecting β-blockers that have a beneficial effect on PWV and the augmentation index will lead to an even better long-term outcome.

Other antihypertensive drugs

The effects of different antihypertensive drugs on the distensible properties of the arterial tree are varied, with some having greater effects than others, independent of the magnitude of blood pressure reduction [70]. For example, although fosinopril and atenolol reduce ambulatory blood pressure to a similar degree, fosinopril has a much greater beneficial effect on the augmentation index than has atenolol [72]. This result may be less interesting than it initially seems, as the apparent disadvantage held by atenolol could well be due to the decrease in heart rate seen with this drug.

Reduction of blood pressure *per se* is associated with an improvement in outcome; however, large outcome trials have suggested that some antihypertensive agents are better than others at improving outcome. It is of great interest that the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study [73,74] has

shown losartan to be of greater benefit than atenolol with respect to the combined endpoint of cardiovascular events *for the same reduction in blood pressure*. When this endpoint is broken down, it is seen that the cause of this improved outcome with losartan is a reduction in cerebrovascular events, rather than cardiovascular events. It may be that the main protective effect of atenolol lies in its myocardium-protective, anti-ischaemic effects, whereas losartan has greater vascular protective effects on both the coronary arteries and the cerebrovasculature. The beneficial effect of atenolol on the myocardium may counterbalance the beneficial effect of losartan on the coronary arteries and explain why the cardiac events in the LIFE study were no different between the two treatments. However, the vasculoprotective effect of losartan may predominate in the cerebrovasculature and explain why losartan was better at preventing strokes. It is not known whether losartan does bring about a decrease in PWV and the augmentation index; however, the earlier study comparing the effects of atenolol and fosinopril on the augmentation index [72] certainly makes this theory attractive. Indeed, if it were shown that agents that exerted a better effect on survival had more of a beneficial effect on arterial stiffness, then arterial stiffness could become a useful therapeutic target and a useful surrogate by which to judge potential new therapies.

Antioxidants

Antioxidants such as vitamins E and C and allopurinol (a xanthine oxidase inhibitor) have potential beneficial effects on the cardiovascular system. The main reason for this is believed to be an improvement in endothelial function secondary to decreased nitric oxide degradation by free radicals. Unfortunately, even though these substances improve endothelial function [75–79], the evidence of benefit in large outcome trials is mixed. The Heart Outcomes Prevention Evaluation study and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico trial failed to show any long-term benefit of chronic ingestion of vitamin E [61,80], although chronic administration of this vitamin was seen to decrease the rate of non-fatal myocardial infarction at 1 year in patients with angiographically proven coronary vascular disease [81] and administration of high-dose vitamin E decreases the incidence of cardiovascular disease in patients receiving haemodialysis [82]. It therefore remains unknown whether the facts that vitamin E has been shown to improve arterial compliance and that vitamin C is acutely associated with a decrease in the augmentation index are or are not useful supporting arguments for using PWA/PWV [83,84]

Longitudinal studies

The best evidence for the usefulness of PWA/PWV will only come from longitudinal studies. Only if these studies show that the augmentation index or PWV are predictive of future events and are either better than or a useful addition to traditional cardiovascular risk factors will it be justifiable to use them in clinical practice.

There are some cohort studies looking at the information obtained from applanation tonometry, but many more patient groups will need to be studied to allow us to assess the true value of PWA. However, the body of evidence for using PWV to predict mortality is becoming increasingly convincing.

A few studies have looked at the predictive value of PWA/PWV in patients with hypertension, the elderly and patients with end-stage renal disease. Meaume *et al*. [85] showed, in a cohort of elderly patients, that PWV was the strongest predictor of cardiovascular mortality. However, it has not yet been shown that the augmentation index is any better than pulse pressure in predicting mortality in elderly patients [86]. In patients with end-stage renal disease, the augmentation index and PWV are independent predictors of mortality and have a greater predictive power than has pulse pressure alone [87,88]. Perhaps more importantly, PWV is significantly associated with the occurrence of coronary events in patients with hypertension, even after adjustment for the Framingham score or classic risk factors [89]. This suggests that measurement of PWV may well become a useful tool in assessing risk in patients with hypertension, either on its own or in addition to commonly used risk factors and risk-factor profiles. A recent study has also highlighted the importance of PWV as an independent predictor of mortality (both all-cause and cardiovascular) in patients with type 2 diabetes and impaired glucose tolerance [90].

Conclusion

Non-invasive assessment of the pulse wave using applanation tonometry to measure PWV and the augmentation index is quick and easy to perform, and requires a minimum of training. These techniques may also have a second possible use in the screening of promising new therapies: if treatment-induced changes in PWV and the augmentation index parallel changes in cardiovascular events, then PWV and the augmentation index could be very useful in screening new treatments.

With respect to applanation tonometry, although results tend to be initially promising, several issues need to be addressed before it can be said to be reliable as both a clinical and a research tool. First, there is confusion as to whether heart rate should be controlled for when the augmentation index is calculated. It is particularly concerning that β-blockers and a slow resting heart rate

increase the augmentation index despite their clinical benefit. These examples would suggest that heart rate needs to be controlled for, but may lead to the eventual conclusion that PWV is a much better marker of vascular stiffness than is the augmentation index. A second issue concerns the site of measurement of PWV. As the brachial artery is not subject to overt atherosclerosis, it may be advisable to study PWV in the arteries of the lower limb, which are well known to be affected by atherosclerosis.

The predictive value of PWV is becoming increasingly recognized. However, evidence that PWV can be used to provide a reliable assessment of treatment response is still lacking. There needs to be much more evidence supporting the use of the augmentation index, both for prediction of future events and for assessing treatment response, before it becomes as widely used as its proponents are advocating. Thus, before either of these measurements enters general clinical practice to aid in risk stratification, they need to be properly assessed in large longitudinal follow-up studies involving different groups of patients.

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