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Frontiers in Research Review: Arterial Function

ARTERIAL STIFFNESS AND CARDIOVASCULAR OUTCOME

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SUMMARY

1. Studies have reported an association between arterial function indices and cardiovascular risk factors, as well as the risk of incident cardiovascular events, including coronary heart disease and stroke.

2. The data are overwhelmingly in favour of an independent role for aortic pulse wave velocity in predicting fatal and non-fatal cardiovascular events in healthy and diseased populations and in the evaluation of cardiovascular risk.

3. Augmentation index may independently predict all-cause mortality and cardiovascular events in coronary and end-stage renal disease patients, but some outcome studies have questioned its usefulness in hypertensive subjects and dialysis patients.

4. Systemic arterial compliance, to this time, has not been shown to independently predict cardiovascular outcome.

5. Future cardiovascular risk is greatly modified by prior disease and risk factors; the greatest additional value in measuring arterial stiffness and compliance may be in those with little or no end-organ disease.

Key words: arterial compliance, arterial stiffness, augmentation index, cardiovascular events, cardiovascular risk, pulse wave velocity.

INTRODUCTION

Arteries are a unique system of distensible conduits that contain the pulsatile output of the heart and provide continuous flow to tissues. During systole, the transmitted flow of blood from the heart generates a pressure wave that is propagated to all arteries of the body. The forward pressure wave travels quickly at 5–15 m/s; the speed of transmission of the pressure wave is much faster than that of blood flow. On arrival at branch points or sites of impedance mismatch, the pressure wave is reflected and returned to the heart. The reflected pressure wave usually arrives back at the heart during diastole and is either merged with the pulse that generated it or seen soon after it. If the heartbeat is rapid, the reflected wave may be carried over to the next pulse. In the periphery, the reflected wave results in amplification of the pulse pressure. The form of the pulse wave is a product of ventricular contraction and the compliance of the vascular system; the effects of ageing and disease states can alter it. The timing of ventricular contraction is also important.

In pathological states, loss of elasticity of the large central arteries leads to the process of stiffening of the arterial network termed 'arteriosclerosis' and seen with normal ageing. Macroscopically, the arteries appear tortuous and dilated. Microscopically, there is loss of the orderly elastic lamellae and disorganized thickening of the media with glycosaminoglycan deposition, fibrosis and calcification. In the extreme, there is medial necrosis and aneurysm formation.

With this understanding in mind, the recent evaluation of arterial mechanical properties has included assessment of regional and systemic indices of arterial stiffness and compliance, such as carotid or aortic distensibility, pulse wave velocity (PWV), systemic arterial compliance (SAC) and augmentation index (AI_x). Many studies have reported an association between these indices and cardiovascular risk factors, as well as the risk of incident cardiovascular events, including coronary heart disease and stroke. Some have also reported an important role for these indices in the future prediction of cardiovascular risk. As a consequence, the application of these indices as surrogate end-points or therapeutic targets in epidemiological studies and clinical trials has become widespread. In the present paper, we review the role for assessment of indices of arterial stiffness and compliance in predicting cardiovascular outcome.

PULSE WAVE VELOCITY

Pulse wave velocity is defined as the speed of travel of the pressure pulse along an arterial segment and can be obtained for any arterial segment accessible to palpation. To measure PWV, continuous pulse wave signals are recorded with pressure tonometers positioned over the arterial pulses. When positioned at both the base of the right common carotid artery and over the femoral artery, or over the femoral artery and the ipsilateral dorsalis pedis artery, measurements for both the aorto–femoral (PWV(a–f)) and femoral–dorsalis pedis arterial segments (PWV(f–d)) are obtained. Distances between sampling sites are measured as straight lines between the points on the body surface. The low point of the pulse wave, defined as the point of

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Table 1 Outcome studies of pulse wave velocity

Aortic PWV (rate of change)	Study population	Sample size (*n*)	Outcome (no. events)	Hazard ratio	95% CI	*P* value
1 m/s increase[5]	Elderly subjects	141	CV mortality (27)	1.19	1.03–1.37	0.016
1 log [PWV] unit[6]	Elderly subjects	2488	CV mortality (111)	1.80	1.10–2.80	< 0.05
Lowest to highest tertile[7]	Elderly subjects	2835	Coronary heart disease (101)	2.45	1.29–4.66	0.02
			Stroke (63)	2.28	1.05–4.96	0.03
5 m/s increase[12]	Hypertensive subjects	1980	All-cause mortality (107)	1.34	1.04–1.74	0.02
			CV mortality (46)	1.51	1.08–2.11	0.03
3.5 m/s increase[10]	Hypertensive subjects	1045	Coronary event (53)	1.34	1.01–1.79	0.039
4.0 m/s increase[35]	Hypertensive subjects	1715	Stroke mortality	1.72	1.48–1.96	< 0.001
1 m/s increase[11]	Diabetic and glucose intolerant subjects	571	All-cause mortality (219)	1.08	1.03–1.14	0.001
1 m/s increase (> 12.0 *vs* < 9.4 m/s)[2]	ESRD subjects	241	All-cause mortality (73)	1.39	1.19–1.62	N/A
			All-cause mortality (73)	5.4	2.4–11.9	0.0004
			CV mortality (48)	5.9	2.3–15.5	0.002
1 m/s increase[4]	ESRD subjects	267	Overall mortality (81)	1.15	1.03–1.29	< 0.05
			CV Mortality (36)	1.18	1.01–1.39	< 0.05
Positive *vs* negative change (1 m/s decrease)[13]	ESRD subjects	150	All-cause mortalty (59)	2.59	1.51–4.43	< 0.001
			CV mortality (40)	2.35	1.23–4.51	0.01
			All-cause mortality (59)	0.71	0.60–0.86	N/A
			CV mortality (40)	0.79	0.69–0.93	N/A
1 m/s increase (> 9.9 *vs* < 9.9 m/s)[8]	Healthy subjects	492	CV mortality (14)	1.35	1.12–1.57	< 0.01
			CV mortality (14)	4.24	1.39–12.96	< 0.01
3.4 m/s increase[9]	Healthy subjects	1678	CV mortality (62)	1.20	1.01–1.41	< 0.05
			CHD (101)			

PWV, pusle wave velocity; CV, cardiovascular; ESRD, end-stage renal disease; CHD, coronary heart disease; CI, confidence interval; N/A, not available.

intersection of the end of diastole and beginning of systole, is identified from the waveform analysis as the maximum of the first derivative at the pressure signal. The mean transit time (Δt) between the feet of two simultaneously recorded waves is then determined from 10 consecutive cardiac cycles and PWV calculated from the distance between measurement points and the time delay (Δt) as follows:

$$PWV = D/\Delta t \ (m/s)$$

where D is distance in metres and Δt is the time interval in seconds.

Pulse wave velocity has been studied widely in healthy and diseased populations and related to cardiovascular risk. A summary of the prospective outcome studies reporting PWV is provided in Table 1.

Aortic PWV was first studied prospectively in patients with end-stage renal disease on haemodialysis. In such patients, aortic PWV was significantly greater than in healthy controls[1] and an independent predictor of all-cause and cardiovascular mortality.[2] Aortic PWV was also independently and positively correlated with age, systolic blood pressure, aortic calcification and diabetic state.[3] A similar study of 265 Japanese haemodialysis patients also found aortic PWV to be a significant predictor of cardiovascular and overall mortality in a model including age, diabetes, C-reactive protein, serum creatinine, total protein and systolic and diastolic blood pressure.[4] However when high-density lipoprotein–cholesterol (HDL-C) and non-HDL-C were added to the model, aortic PWV was no longer a significant predictor of cardiovascular mortality, suggesting an interaction between conventional cardiovascular risk factors and aortic PWV.[4]

Studies of healthy populations have also reported an association between aortic PWV and cardiovascular outcome. In 2001, a study of older patients (> 70 years) by Meaume *et al*. reported that aortic PWV was an independent predictor of cardiovascular mortality[5] and was followed by the Health ABC study.[6] That study separated its population into quartiles of aortic PWV and showed that the risk of all fatal and non-fatal cardiovascular events increased with increasing quartile, with a threshold effect seen between the first and second quartile.[6] More recently, the Rotterdam study of apparently healthy, older subjects also reported that aortic PWV was an independent predictor of coronary heart disease and stroke.[7] However, in that study the additional predictive value of aortic PWV was only small (area under the receiver–operator curve (ROC) curve 0.70–0.72) after accounting for other cardiovascular risk factors, measures of atherosclerosis and pulse pressure.

Two population-based studies of younger subjects have also examined the role of aortic PWV as an independent predictor of cardiovascular outcome.[8,9] Both studies have similarly found aortic PWV to be an independent predictor of cardiovascular events. In one study of Japanese Americans, the relative risk associated with increased aortic PWV for cardiovascular mortality was 4.24 (95% confidence interval (CI) 1.39–12.9) after adjusting for age, gender, systolic blood pressure, diabetes, hyperlipidaemia and electrocardiogram (ECG) changes.[8] That study also reported the observed optimum threshold for aortic PWV as 9.9 m/s, but was heavily criticised for its post hoc nature and small number of events ($n = 43$), of which only 14 were cardiovascular deaths. However, a subsequent Danish study of 1678 people aged between 40 and 70 years has provided further supportive data.[9] After adjusting for pulse pressure and mean arterial pressure, that study found that for each 1 standard deviation increase in aortic PWV (3.4 m/s), the risk of a cardiovascular event increased by 16–20%.

Table 2 Outcome studies of augmentation index

AI_x (rate of change)	Study population	Sample size (*n*)	Outcome (no. events)	Hazard ratio	95% CI	*P* value
Each 10% increase[16]	ESRD subjects	180	CV mortality (40)	1.48	1.16–1.90	< 0.0001
			Total mortality (70)	1.51	1.23–1.86	< 0.0001
Lowest to highest tertile[19]	CHD subjects	262	Death, AMI, coronary restenosis (61)	1.80	1.18–2.76	0.006
Intra-aortic AI_x (each 10% increase)[20]	CHD subjects	297	Major CV events or death (N/A)	1.28.	1.09–1.50	0.003
Upper to lower half[21]	Hypertensive subjects	484	CV events (53)	0.80	0.44–1.44	
Lowest to highest tertiles[23]	ESRD subjects	92	Total mortality (15)	N/A	N/A	0.78

AI_x, augmentation index; CV, cardiovascular; ESRD, end-stage renal disease; CHD, coronary heart disease; AMI, acute myocardial infarct; CI, confidence interval; N/A, not available.

The observations are similar in hypertensive and diabetic/glucose-intolerant subjects, with studies finding aortic PWV to be an independent predictor of primary coronary events[10] and/or all-cause and cardiovascular mortality.[11,12]

To date, only one study has examined whether PWV is amenable to therapy and can be lowered to improve cardiovascular outcomes.[13] That study, by Guerin *et al*., examined the relationship between aortic PWV and all-cause and cardiovascular mortality in response to blood pressure lowering in 150 patients with end-stage renal disease.[13] The authors found that the predictors of all-cause and cardiovascular mortality were an absence of a decrease in PWV in response to a decrease in blood pressure, increased left ventricular mass, age and pre-existing cardiovascular disease. After adjustment for all confounding factors, the risk ratio for the absence of a decrease in PWV was 2.59 (95% CI 1.51–4.43) for all-cause mortality and 2.35 (95% CI 1.23–4.41) for cardiovascular mortality. These treatment effects seem promising, but remain to be seen in other populations.

AUGMENTATION INDEX

The AI_x represents the timing of pressure wave reflection in relation to left ventricular systolic pressure and is calculated as the ratio of the pressure difference between the shoulder of the wave and peak systolic pressure (ΔP) and the pulse pressure (PP) according to the formula:

$$AI_x = (\Delta P/PP) \times 100$$

Measurement can involve directly obtaining either carotid artery or ascending aortic waveforms to identify the 'shoulder' and 'peak' of the waves, or using a transfer function to derive aortic pressure waveforms from recorded radial artery waveforms.[14]

The AI_x has been related to previously mortality and cardiovascular events in patients with end-stage renal disease and those undergoing percutaneous coronary intervention. A summary of the prospective outcome studies reporting AI_x is provided in Table 2.

Marchais *et al*. first described increased arterial wave reflections and carotid artery AI_x in haemodialysis patients in 1993[15] and followed this some years later with a prospective study of 180 dialysis patients.[16] That study found that AI_x was independently predictive of all-cause and cardiovascular mortality (odds ratio (OR) 1.51 (95% CI 1.23, 1.86; $P < 0.0001$) and OR 1.48 (95% CI 1.16, 1.90; $P < 0.0001$), respectively).[16] Nurnberger later found that carotid artery AI_x was significantly increased with increasing cardiovascular risk scores and correlated to cardiovascular risk.[17] Similarly, Weber *et al*. showed that ascending aortic AI_x derived from the radial artery was associated with an increased risk for coronary artery disease (unadjusted OR 4.06 ($P < 0.01$ for the difference between the first and the fourth quartile) and OR after controlling for age, height, presence of hypertension, HDL-C and medications 6.91 ($P < 0.05$)).[18] More recently, Weber *et al.* have reported radial artery derived AI_x to be predictive of death, myocardial infarction and clinical restenosis (relative risk 1.8 per increasing AI_x tertile; 95% CI 1.18–2.76; $P = 0.006$) in a 2 year prospective study of 262 patients undergoing percutaneous coronary intervention.[19] Another invasive study of intra-aortic AI_x in male patients with established coronary disease also found that AI_x predicted major adverse cardiovascular events.[20]

In contrast, the Australian National Blood Pressure Study 2 (ANBP2) of 484 elderly hypertensive women found that AI_x did not independently predict cardiovascular disease -ree survival,[21] although there was a trend for fewer events with increased AI_x. The authors did suggest that this may have been because of the lower discriminatory value of AI_x in this older cohort (> 70 years) with hypertension and a low prevalence of known vascular disease. The important confounding effect of age on AI_x has been highlighted previously by a study by McNiery *et al*., who found thatm after 55 years of age, AI_x changed very little.[22] Another albeit smaller study of younger haemodialysis patients similarly reported that AI_x did not independently predict total mortality.[23]

The predictive value of radial artery derived AI_x has also been examined by the recent CAFE (Conduit Artery Function Evaluation) substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).[24] In that study, AI_x was not predictive of the primary composite cardiovascular and renal end-point.

SYSTEMIC ARTERIAL COMPLIANCE

Arterial compliance represents the relationship between change in volume and change in pressure during diastole and is a direct measure of the elastic nature of the vasculature. As compliance increases, the change in volume required to produce a unit change in pressure is increased. The SAC is one expression of this exponential relationship and is estimated using the 'area method'. The SAC requires measurement of volumetric blood flow and associated driving pressure to derive an estimated compliance over the total systemic arterial tree. A hand-held Doppler flow velocimeter placed on the suprasternal notch at the base of the neck is used to estimate arterial blood flow. Aortic driving pressure is estimated by applanation tonometry of the

right common carotid artery using a non-invasive pressure transducer. The SAC is then calculated according to the formula:

$$SAC = Ad/R(Pes - Pd)$$

where R is total peripheral resistance calculated as mean arterial blood pressure/mean blood flow, Ad is the area under the diastolic portion of the pulse pressure contour, Pes is end-systolic aortic blood pressure and Pd is end-diastolic arterial blood pressure.

Systemic arterial compliance has not been studied as extensively as PWV or AI_x. One study of patients newly diagnosed with coronary heart disease found that SAC was decreased, whereas regional wall stiffness was increased, in patients with known coronary disease compared with controls.[25] In another study of healthy post-menopausal women, SAC was inversely related to ag, but also positively related to treatment with hormone-replacement therapy.[26,27]

The ANBP2 was the first prospective study to report the usefulness of SAC in predicting outcome in elderly hypertensive women.[21] After adjusting for age, cholesterol and smoking history, SAC was not an independent predictor of outcome.

ARTERIAL DISTENSIBILITY

The distension of an artery refers to the change in diameter during systole relative to diastole. Lower distension suggests regional arterial stiffening. Ultrasound measurements of the distal common carotid artery or aorta during the cardiac cycle can be used to determine wall displacement and, thus, artery distension.

Common carotid artery and aortic distensibility have been studied and related to all-cause mortality and cardiovascular events. However, all studies have been limited by small numbers. Blacher *et al*. related carotid stiffness to total mortality in a study of 79 haemodialysis patients[28] and Barenbrock *et al*. reported an independent association with cardiovascular events in a study of 68 renal transplant recipients.[29] With respect to aortic distensibility, Stefanidis *et al*. studied 54 patients with coronary artery disease and reported that increased aortic distensibility was associated with reduced coronary risk.[30] More recently, carotid artery stiffness has also been assessed in the Second Manifestations of ARTerial disease (SMART) study. This study has reported an inverse relationship between carotid distension and prevalent ischaemic stroke and transient ischaemic attack in patients with a ≥ 50% internal carotid artery stenosis, but no independent predictive role for incident vascular events in a larger study of 2183 patients with manifest arterial disease.[31,32]

COMPARISON OF ARTERIAL FUNCTION MEASURES AS PREDICTORS OF CARDIOVASCULAR OUTCOME

The recently published Atherosclerosis and Folic Acid Supplementation Trial (ASFAST) in patients with end-stage renal disease showed no apparent benefit of high-dose folic acid on cardiovascular morbidity and mortality, or any surrogate index of arterial disease, including intima–media thickneww and PWV.[33] In that study, the predictive value of three baseline arterial function indices (PWV, SAC and AI_x) for cardiovascular outcome were examined in a subgroup of 207 subjects. The results are summarized in Table 3 and show that PWV was the only independent predictor of outcome after adjustment for conventional risk factors.

Table 3 Comparison of arterial function indices as predictors of cardiovascular outcome in the Atherosclerosis and Folic Acid Supplementation Trial (ASFAST)[33]

Parameter	HR (95% CI)	*P* value	Adjusted HR† (95% CI)	*P* value
PWV(a–f)	2.75 (1.72, 4.41)	< 0.001	2.11 (1.18, 3.77)	0.011
SAC	0.65 (0.41, 1.01)	0.058	0.85 (0.52, 1.40)	0.521
AI_x	0.93 (0.60, 1.45)	0.761		

†Adjusted for age, gender, blood pressure, diabetes, past history of cardiovascular disease, cholesterol and smoking.

PWF(a–f), aorto–femoral pulse wave velocity; SAC, systemic arterial compliance; AI_x, augmenation index; HR, hazard ratio; CI, confidence interval.

CONCLUSIONS

The data are overwhelmingly in favour of an independent role for aortic PWV in predicting fatal and non-fatal cardiovascular events in healthy and diseased populations and in the evaluation of cardiovascular risk. The AI_x may independently predict all-cause mortality and cardiovascular events in coronary and end-stage renal disease patients. However, recent outcome studies have questioned its usefulness in hypertensive subjects and dialysis patients. More prospective data from the general population and diseased groups are required to define the prognostic value of AI_x for cardiovascular outcome as reflected in the recent consensus document on arterial stiffness published on behalf of the European network for non-invasive investigation of large arteries.[34] The studies to date reporting the predictive value of SAC are limited. Systemic arterial compliance may be a useful surrogate end-point for use in longitudinal studies of patients with known coronary disease; however, to measure this index with high precision and good reproducibility is technically demanding and limits its use. The present report highlights that future risk is greatly modified by prior disease and risk factors and that the greatest additional value in measuring arterial stiffness and compliance may be in those with little or no end-organ disease.

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