

## HYPERTENSION AND MACROVASCULAR DISEASE

Stephane Laurent, MD, PhD, Department of Pharmacology, Pitié-Salpêtrière Hospital, Inserm U652 and University Paris Descartes, France

Arterial stiffness and wave reflection are now well-accepted as the most important determinants of increasing systolic and pulse pressures in ageing societies, thus promoting a major contribution to stroke and myocardial infarction. A major reason for measuring arterial stiffness and central pulse pressure (PP) in hypertensive patients comes from the demonstration that arterial stiffness and central PP have a predictive value for cardiovascular events. A recent expert-consensus document has reviewed the methodological agreements for measuring arterial stiffness and wave reflections [1]. This newsletter will not address the issue of intima-media thickness (Newsletter n°15) and endothelial dysfunction.

### Methods of measurement

Large artery damage in hypertension can be non-invasively assessed through the measurement of arterial stiffness, central pulse pressure (PP) and central augmentation index (AIx) (Table 1). In contrast to systemic arterial stiffness, which can only be estimated from models of circulation, regional and local arterial stiffness can be measured directly and non-invasively at various sites along the arterial tree.

The measurement of pulse-wave velocity (PWV) is generally accepted as the most simple, non-invasive, robust and reproducible method with which to determine arterial stiffness [1]. Carotid-femoral PWV is a direct measurement of aortic stiffness, and it corresponds to the widely accepted propagative model of the arterial system. Measured along the aortic and aorto-iliac pathway, it is the most clinically relevant, since the aorta and its first branches are what the left ventricle 'sees', and are thus responsible for most of the pathophysiological effects of arterial stiffness. PWV is usually measured using the foot-to-foot velocity method [1, 2].

Local arterial stiffness of superficial arteries can be determined using ultrasound devices [3]. Carotid stiffness may be of particular interest, since in such arteries atherosclerosis is frequent. A major advantage is that local arterial stiffness is directly determined from the change in local pressure driving the change in volume and thus without using any circulatory model. However, because it requires a high degree of technical expertise and takes longer than measuring PWV, local measurement of arterial stiffness is only really indicated for mechanistic analyses in pathophysiology, pharmacology and therapeutics rather than for routine use [1].

Arterial pressure waveform should be analysed at the central level, at the ascending aorta, since it represents the true load imposed on the left ventricle and central large artery walls. Aortic pressure waveform can be estimated either from the radial artery waveform, using a transfer function [4], or from the common carotid waveform, using aplanation tonometry [5]. The arterial pressure waveform is a composite of the forward pressure wave created by ventricular con-

traction and a reflected wave. In the case of stiff arteries, PWV rises and the reflected wave arrives back at the central arteries earlier, adding to the forward wave and augmenting the systolic pressure. This phenomenon can be quantified through the augmentation index (AIx), defined as the difference between the second and first systolic peaks expressed as a percentage of the PP [4, 5].

### The pathophysiology of cardiovascular events

A generally-accepted mechanistic view is that an increase in arterial stiffness causes a premature return of reflected waves in late systole, increasing central PP and thus SBP. SBP increases the load on the left ventricle, increasing myocardial oxygen demand. In addition, arterial stiffness is associated with left ventricular hypertrophy, a known risk factor for coronary events, in normotensive and hypertensive patients. The increase in central PP and the decrease in diastolic blood pressure may directly cause subendocardial ischaemia.

An increased arterial stiffness can augment the risk of stroke through several mechanisms, including an increase in central PP, influencing arterial remodelling at the site of both the extracranial and intracranial arteries, increasing carotid wall thickness and the development of stenosis and plaques as well as the likelihood of plaque rupture and the prevalence and severity of cerebral white matter lesions. Finally, coronary heart disease and heart failure, which are favoured by high PP and arterial stiffness, are also risk factors for stroke.

### The predictive value of arterial stiffness and central PP

Table 2 summarises the longitudinal epidemiological studies which have demonstrated the independent predictive value of arterial stiffness, carotid PP and the augmentation index for cardiovascular events. The largest amount of evidence has been accumulated for aortic stiffness, measured through carotid-femoral PWV. Aortic stiffness has independent predictive value for all-cause and cardiovascular mortality, fatal and non-fatal coronary events and fatal strokes in patients with uncomplicated essential hypertension [6–8], type 2 diabetes [9] and end-stage renal disease [10, 11], as well as elderly subjects [12, 13] and the general population [14–16]. It is now well-accepted that aortic stiffness is an intermediate endpoint for cardiovascular events. The independent predictive value of aortic stiffness has been demonstrated after adjustment for classical cardiovascular risk factors, including brachial PP. This indicates that aortic stiffness has a better predictive value than each of the classical risk factors. Although the relationship between aortic stiffness and events is continuous, a threshold > 12 m/sec has been suggested as a conservative estimate of significant alterations of aortic function in middle-age hypertensives [6–8]. High aortic PWV may thus represent target organ damage, which needs to be detected during estimation of cardiovascular risk in hypertensives.

Central AIx and PP, either directly measured by carotid tonometry [17, 18] or estimated using a transfer function from radial artery tonometry [19], are both independent predictors of all-cause mortality in end-stage renal disease patients [17, 18], and cardiovascular events in patients undergoing percutaneous coronary intervention [20, 21] and in the hypertensive patients of the CAFÉ study [19]. However, the prognostic role of central SBP and PP vis-à-vis the peripheral ones needs to be further demonstrated in large-scale observational and intervention studies.

### Clinical application

Non-pharmacological treatments which are able to reduce arterial stiffness and/or central PP and AIx include exercise training, dietary changes (including weight loss, a low-salt diet, moderate alcohol consumption, dark chocolate, garlic powder, alpha-linoleic acid and fish oil) and hormone replacement therapy (HRT) [1].

Antihypertensive treatments are able to reduce arterial stiffness mainly through the lowering of mean blood pressure, thus reducing the load on the arterial wall [1]. The reduction in wave

Table 1. Methods for measuring arterial stiffness in clinical investigation (Adapted from ref. 1)

Parameter	Predictive value for CV events	Degree of technical expertise
<b>Carotid-femoral PWV</b>	+++	+
Gold standard for arterial stiffness Speed of travel of the pulse along an arterial segment (L/Dt in m/s)		
<b>Central pulse wave analysis</b>	++	+
Carotid and aortic pressure waves Central pulse pressure (PP) and SBP Central augmentation index (AIx)		
<b>Local arterial stiffness</b>	+	+++
Carotid distensibility		

Table 2. Longitudinal studies reporting the independent predictive value of aortic stiffness and central pressure (Adapted from ref. 1)

Measurement site, ref.	Events	Follow-up (years)	Type of patient (number)	Mean age at entry (years)
<b>Aortic PWV</b>				
Blacher et al. 1999	CV mortality	6.0	ESRD (241)	51
Laurent et al. 2001	CV mortality	9.3	Hypertension (1980)	50
Meaume et al. 2001	CV mortality	2.5	Elderly (>70) (141)	87
Shoji et al. 2001	CV mortality	5.2	ESRD (265)	55
Boutouyrie et al. 2002	CHD events	5.7	Hypertension (1045)	51
Cruickshank et al. 2002	All cause mortality	10.7	IGT (571)	51
Laurent et al. 2003	Fatal strokes	7.9	Hypertension (1715)	51
Sutton-Tyrrell et al. 2005	CV mortality and events	4.6	Elderly (2488)	74
Shokawa et al. 2005	CV mortality	10	General population (492)	64
Hansen et al. 2006	CV mortality	9.4	General population (1678)	55
Mattace-Raso et al. 2006	CV mortality, CHD	4.1	Elderly (2835)	72
<b>Central pulse pressure/augmentation index</b>				
London et al. 2001	All cause and CV mortality	4.3	ESRD (180)	54
Safar et al. 2002	All cause mortality	4.3	ESRD (180)	54
Weber et al. 2005	Severe CV events	2	CHD undergoing PCI (465)	66
Chirinos et al. 2005	CV events	3.5	CHD undergoing PCI (297)	64
Williams et al. 2006	CV events	3.4	HT, ASCOT study (2073)	63

PWV: pulse wave velocity; ESRD: end-stage renal disease; IGT: impaired glucose tolerance; CHD: coronary heart disease; PCIs: percutaneous coronary intervention

reflections through peripheral vasodilatation associated with the reduction in aortic stiffness represents a means to lower central PP and/or Alx. This has been shown to various extents for diuretics, beta-blockers, ACE inhibitors, AT1 blockers, calcium channel antagonists, centrally-acting agents, peripheral vasodilators and alpha-blockers. Several studies, including the CAFÉ and REASON studies [19, 22], have shown that the effects of antihypertensive drugs on central systolic and pulse pressures do not invariably reflect those obtained at brachial artery level. They suggest that clinical outcomes should be related to the antihypertensive effect observed at the central level rather than at the brachial level.

### Conclusion

These data highlight the importance of arterial stiffness and wave reflection for predicting cardiovascular outcomes. Arterial stiffening also

provides direct evidence of target organ damage, which is of major importance in determining the overall cardiovascular risk of the hypertensive patient. Indeed, measurement of aortic stiffness and central PP and Alx may exclude patients mistakenly classified as at low or moderate risk, when they actually have an abnormally high aortic stiffness or central PP and Alx, placing them within a higher risk group.

Several issues remain to be addressed. Of these a crucial one is to determine whether a reduction in arterial stiffness is a desirable therapeutic goal in terms of hard clinical endpoints such as morbidity or mortality. Although this has been done in patients with end-stage renal disease [23], it remains to be shown in a population of hypertensive patients at lower cardiovascular risk. In addition, it is important to demonstrate whether a therapeutic strategy aiming at normalising arterial stiffness and wave reflection proves to be more effective in preventing cardiovascular events than usual care.

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