

Arterial aging: principles and implications for monitoring and therapy

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Subtly, over recent years in Western countries, there has been a change in the type and presentation of cardiovascular disease¹⁻⁴. While coronary artery disease remains a major cause of death and disability and is increasing in developing countries as those become more affluent, the peak of the epidemic has passed. In its place other problems have arisen, and other epidemics are now with us – of cardiac failure, renal failure and dementia. These problems are usually seen in older persons, and more often in women than men. All appear to be related to another type of arterial disease, which stiffens rather than obstructs the major arteries^{5,6}. Attention is now being directed at this, and how it might be prevented, delayed, or treated.

Basically, the problem is with arterial stiffening with age. One hundred years ago, William Osler described this as senile arteriosclerosis, and distinguished it from atherosclerosis, which he called nodular arteriosclerosis⁷. Other luminaries of the time described ill effects on the heart as a consequence of arterial stiffening⁸, and the cardiac decompensation and failure that resulted⁹. At the time, presence of senile arteriosclerosis was assessed from contour of the radial artery pressure waveform, rather than from brachial cuff blood pressure, and such pulse waveform analysis was used to detect premature arterial degeneration, and even to decline applicants for life insurance¹⁰. Over the subsequent century, the cuff sphygmomanometer has been used almost exclusively to assess the development of arteriosclerosis, but proved misleading, since at least until SHEP trial in 1991¹¹, fall in diastolic pressure was considered innocuous, and rises in systolic and pulse pressure were disregarded. The Framingham Heart Study has provided the best epidemiological information on this condition, showing progressive rise in systolic and pulse pressure

with age and fall of diastolic pressure and the ill effects of such change^{12,13}.

Arterial aging is described in a number of recent books and reviews^{5,6,14,15}. It occurs independently of atherosclerosis, and in societies with low prevalence of atherosclerosis. It can occur prematurely in some families and it is accelerated by such conditions as diabetes mellitus and hypertension^{5,6}. Its principal manifestations are change in shape of the arterial pressure wave with increase in systolic and pulse pressure (and fall in diastolic pressure). Aortic dilation may be seen in chest x-rays. Onset is insidious. Persons are initially well but gradually, cardiac enlargement and failure develops, then renal failure and intellectual deterioration.

The basic cause of arteriosclerosis appears to be fatigue and then fracture of elastin lamellae in the aorta and major proximal arteries^{5,6,14}. With fracture of elastin there is disorganisation of the arterial media; the aorta dilates and fibrous remodelling occurs. The aorta stiffens because stresses are borne by less extensible collagenous fibres. The proximal aorta and elastic arteries are more affected than distal muscular arteries because these have been stretched more by repetitive pulsations in previous years (the aorta by around 10%, the brachial by 3%). Changes can be explained on the basis of standard engineering principles of material fatigue and fracture⁵.

Arterial stiffening can be measured in a number of ways. Favoured by European consensus groups¹⁶ are measures of aortic pulse wave velocity, analysis of the pulse waveform, and local determination of arterial elasticity. Indices so obtained have been considered for use in guidelines for treatment of hypertension by the European Society of Hypertension (ESH) and European

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Society of Cardiology (ESC)¹⁷, are likely to be further endorsed at the 2007 meetings of ESH and ESC.

The effects of aortic stiffening on the heart are explicable on the basis of a direct and indirect effect – by increase in the initial pressure wave generated by the left ventricle (LV), and by early return of wave reflection from peripheral sites^{5,6,15}. Early return of wave reflection causes a boost of pressure during late systole, rather than boosting pressure throughout diastole, as in youth. The summed effect is to increase aortic and left ventricular pressure during systole, leading to LV hypertrophy and eventually to LV failure¹⁵. There is also predisposition to myocardial ischaemia on account of lower coronary perfusion pressure during diastole and reduced diastolic perfusion time (as a consequence of LV hypertrophy). Imbalance between myocardial oxygen demands and supply is worsened by tachycardia, since there is relative preservation in duration of systole but reduction in diastolic period^{5,15}. These are the mechanisms which underlie the problem of “diastolic” heart failure in the elderly, and which make older people, particularly women, susceptible to angina pectoris even in the absence of coronary disease⁵.

It is only recently that the link between arterial stiffening and renal failure and dementia has been identified¹⁸⁻²⁰, and explained^{21,22}. Non-atheromatous disease of tiny arterial vessels appears to be responsible for such conditions. The small artery changes comprise medial disruption with microhemorrhages and intimal denudation with secondary thrombosis and infarction, and are similar to those seen in the lungs of children with congenital left to right shunting as a cause of Eisenmenger’s syndrome²³. This condition in the lungs is attributable to high pressure and flow pulsations damaging the small arterial vessels over many years. Similar changes over years in the cerebral and renal vessels can likewise be attributed to high pressure and flow fluctuations extending further downstream into the small fragile micro vessels as a consequence of failure of the aorta and large elastic arteries to absorb these. The vulnerability of heart and kidneys appears to be related to their high perfusion and low vascular impedance²¹⁻²². LV micro vessels may be spared by contraction of surrounding muscle during systole^{21,22}.

Understanding of mechanisms provides a basis for considering prevention and treatment. There is little one can do when irreversible damage has occurred in the aor-

tic media, just as there is little one can do for irreversible damage to heart, brain, or kidney cells. But one can control wave reflection by use of arterial vasodilating mechanisms. In youth, wave reflection is physiologically useful, since it causes an “echo” in the aorta during diastole – a boost to pressure throughout diastole when the coronary arteries to the LV are perfused⁵. With aortic stiffening, velocity of the pulse wave in the wall increases so that the reflected wave comes in earlier, during systole, leading to the augmentation of pressure during late systole and to the ill effects described above. Vasodilator drugs such as nitrates, calcium channel antagonists, ACE inhibitors and angiotensin receptor blockers markedly reduce wave reflection^{5,6,22}. The principal beneficial effects can be explained on this basis. So can the effects of regular exercise⁵, which improves endothelial function and thereby decreases wave reflection and central systolic pressure. Beneficial effects on wave reflection can explain in large part the value of these drugs in hypertension for delaying target organ damage and cardiovascular events, and in syndromes of myocardial ischaemia and cardiac failure in older persons. In like fashion, one can explain favourable effects on microvascular disease in the brain and kidney, and so prevention or delay in progression of renal failure and intellectual deterioration^{22,24,25}.

Relevance of these principles has been delayed by almost complete dependence on the cuff sphygmomanometer for assessment of aging change and effects of therapy. Recent trials such as REASON²⁶ and the CAFE substudy of ASCOT²⁷ confirm the value of reducing central arterial pressure from use of ACEI/CCB, and the potential hazards of betablocking drugs such as atenolol²⁸. Methods for measuring central aortic pressure are gaining credence, and are likely to be included in future guidelines for assessment and treatment of hypertension and the other problems of arterial degeneration.

Figure 1 provides an example of how one can combine conventional sphygmomanometry with analysis of the pulse waveform in the radial artery. This can readily be applied in office practice, and enables effects of arterial stiffness and wave reflection to be evaluated by the sophisticated physician.

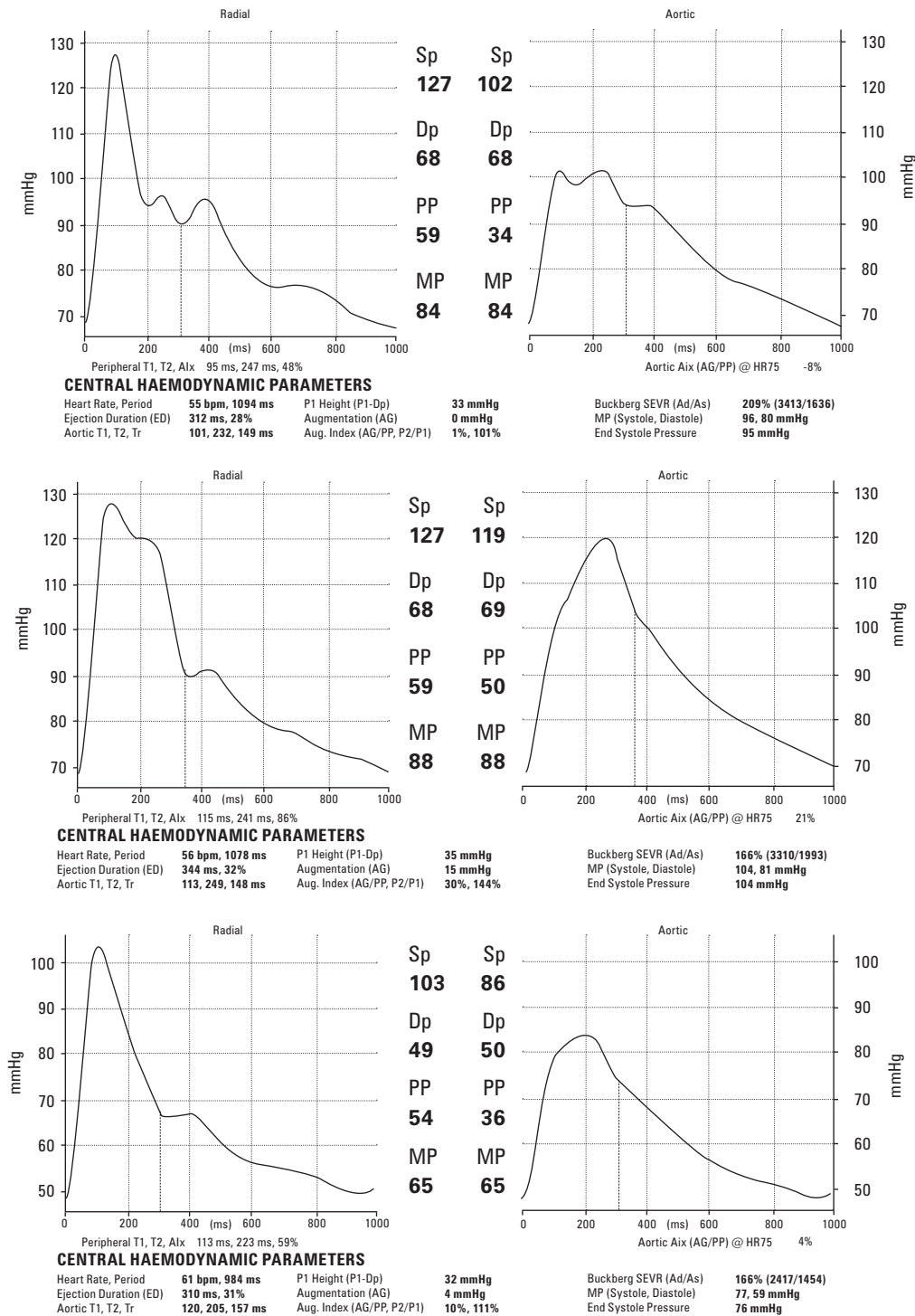


Figure 1. Measured radial (left) and synthesised ascending aortic (right) pressure waves, and their change with age and drug therapy.

Top panel: Waves in a healthy athletic young man, aged 37 years.

Center panel: Waves in his apparently healthy father age 69, with arterial pressure reduced on therapy to the same cuff values, and at similar heart rate. Despite similar brachial systolic pressure, aortic systolic pressure was 17 mmHg lower in the younger man.

Lower panel: Waves in the older man with intensification of ARB therapy from 16 mg to 32 mg candesartan per day. Aortic systolic fell by 11 mmHg more than brachial.

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