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Editorial Comment

Increased arterial stiffness in end-stage renal failure: why is it of interest to the clinical nephrologist?

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Introduction

Hypertension is a cardiovascular risk factor whose adverse effects have been attributed to a reduction in the calibre and/or number of small arteries and arterioles, resulting in increased peripheral vascular resistance. Peripheral vascular resistance and cardiac output are determinants of the mean blood pressure. These indices refer to steady-state phenomena, i.e. pressure and flow are considered as constant over time. This definition does not take into account the fact that blood pressure and flow fluctuate during the cardiac cycle and that, in clinical practice, blood pressure is defined in terms of systolic pressure (SBP) and diastolic pressure (DBP), representing the oscillatory extremes of pulsatile pressure around a mean blood pressure. A more realistic approach is to consider arterial pressure as having a steady component, i.e. mean blood pressure, and a pulsatile component, i.e. pulse pressure [1]. Mean blood pressure is the pressure head for steady flow distribution to the tissues and organs. For a given cardiac output it is determined by the cross-sectional area and the number of arterioles and small arteries. Because ventricular ejection is intermittent, pulse pressure is determined by (i) the pattern of left ventricular ejection, (ii) the viscoelastic properties of large conduit arteries (arterial stiffness), and (iii) the timing of arterial wave reflections.

The increased cardiovascular risk conferred by hypertension would thus be primarily related to three circulatory abnormalities: (i) increased arteriolar resistance, (ii) increased large artery stiffness, and (iii) early wave reflection [1]. This review briefly summarizes the functional characteristics of large arteries and their alterations in diseased humans in general and in patients with end-stage renal disease in particular. Detailed description of these relationships requires considerable mathematical apparatus and is therefore less than popular with clinicians. Yet the basic principles are quite easy to grasp without advanced mathematics and have considerable impact on the rational management of hypertensive patients. In the following we try to outline in simple terms what is relevant for the clinical nephrologist.

Haemodynamic factors governing pulse pressure amplitude

Ejection of blood from the heart into the aorta generates a pressure wave that is propagated to other arteries throughout the body. This forward travelling (incident) pressure wave is reflected at points of structural geometric discontinuity of the arterial tree, generating a reflected 'echo' wave travelling backward towards the ascending aorta. The incident and reflected waves are summed up to yield the pressure wave. As shown in Figure 1, the measured pressure wave is determined by the amplitudes and interaction (timing) of the two component waves. For a given pattern of ventricular ejection the amplitude of the incident pressure wave and the timing of its interaction with the reflected pressure wave depends on the elastic properties of the arterial wall, i.e. on arterial stiffness.

This property of the wall is described by two terms, arterial compliance or distensibility respectively [1,2]. The stiffness of an arterial segment is determined by the changes in circumference or diameter induced by a change in pressure. This is expressed as either compliance or distensibility. The derivation of these terms is described in Figure 2. The pressure diameter relationship is non-linear, so that compliance and distensibility decrease as pressure increases. This is due to the 'two-phase' content of the arterial wall. At lower pressure tension is mainly generated by distensible elastin fibres and at high pressure by less extensible collagen fibres. Increased arterial stiffness, i.e. decreased compliance or distensibility, can be the 'passive' consequence of increased blood pressure, or result from structural or functional alterations of the arterial wall [2]. The most obvious consequence of arterial stiffening on arterial pulse is increased pulse pressure amplitude.

Two mechanisms are involved. The first is a direct mechanism. A higher incident pressure wave is generated by the left ventricle when it has to eject into a 'stiff' arterial system. An increase of the incident wave amplitude is caused not only by a higher peak value, but also as a result of decreased reservoir (or Windkessel) effect. As a result a greater proportion of stroke volume runs off during systole and less blood

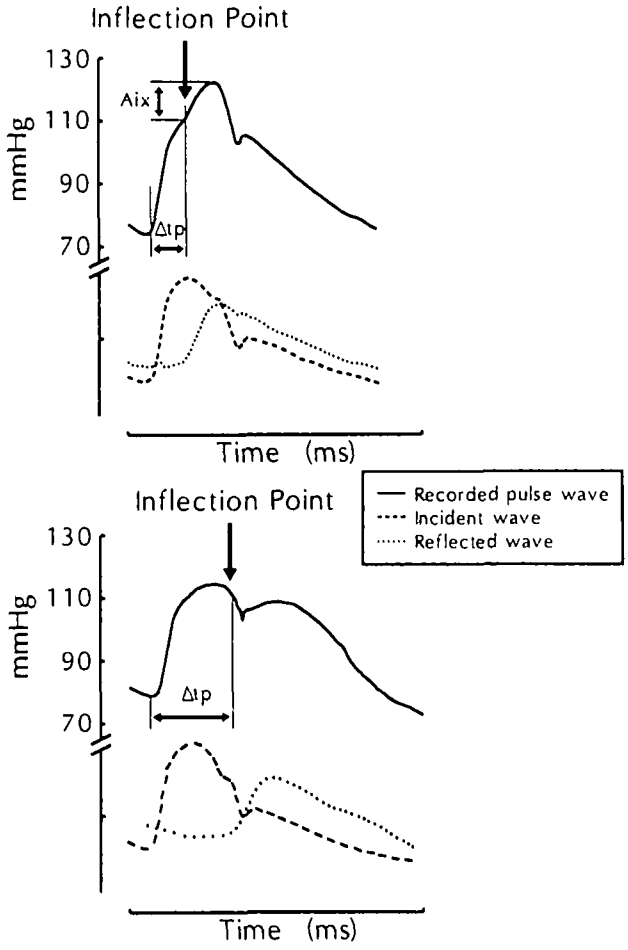

Fig. 1. Recorded, incident and reflected pressure waves in the aorta in an older (upper figure) and younger (lower figure) subject. The algebraic sum of incident and reflected waves yields the recorded pressure wave, on which the reflected wave appears at the inflection point. In this example the contour and amplitude of incident and reflected waves were kept similar, only the travel time of pressure wave to reflecting sites (Δtp) and back changed. In the older subject arterial stiffening increases PWV, shortening Δtp, with reflected wave returning during systolic interval. The result is an increased systolic and pulse pressure (quantified as Aix—amplification index). In the younger subject with distensible arteries, PWV is low and Δtp longer. The reflected wave reaches the aorta during early diastole with no effect on systolic and pulse pressures.

volume is 'drained' during diastole. In addition elastic recoil is diminished. Thus diastolic pressure decreases more rapidly and end-diastolic blood pressure is lower.

The second is an indirect mechanism. Increased arterial stiffness increases the velocity of the pressure wave through systemic arteries. This has repercussions on the timing of incicent and reflected waves.*

The reflected wave travelling backward from the periphery to the heart acts like a counterpulse. Sites of reflection include (i) the parts of the arterial walls with locally increased stiffness, and (ii) arterial/arteriolar junctions where low-resistance arteries terminate in high-resistance arterioles and branching points. Incident and reflected waves are in constant interaction and the amplitude and shape of the measured pulse pressure wave are determined by the phase relationship

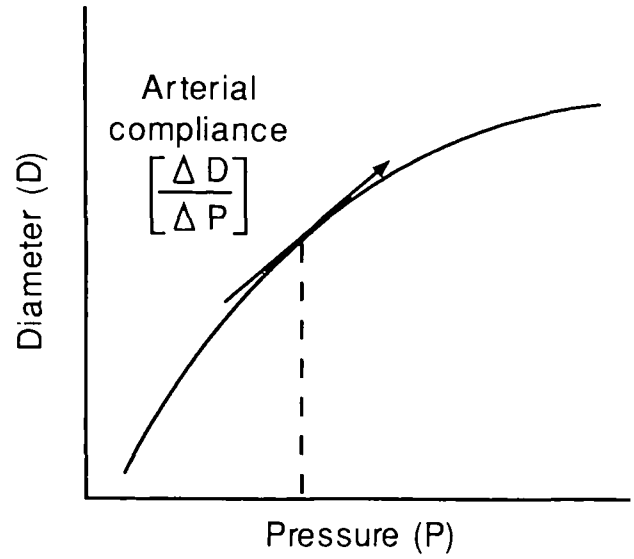

Fig. 2. Schematic representation of the pressure (P)–diameter (D) (or volume) relationship in a given artery. Arterial compliance (C) is defined as the 'slope' D/P of the relationship, i.e. $C = \Delta D/\Delta P$, where ΔD is the change in diameter and ΔP the change in pressure. Arterial distensibility (Di) is defined as $Di = \Delta D/\Delta P \times D$, where D is baseline diameter. Di is an index of the relative change in diameter ΔD/D.

(the timing) between the component waves (Figure 1). Indeed, because pressure waves travel at a finite velocity, the shape and amplitude of measured pressure waves depend on the site of pressure recording in the arterial tree. In peripheral arteries the incident and reflected waves are in phase, producing an additive effect. The ascending aorta and central arteries are distant from the sites of reflection. Consequently, depending on (i) the pulse wave velocity and (ii) the length of the arterial tree, the return of the reflected waves is delayed to a variable extent. The incident and reflected waves are therefore enough in phase.

In young human subjects with distensible arteries and low pulse wave velocity, the reflected waves impact on central arteries during diastole, after ventricular ejection has ceased. Such timing is desirable, since the reflected waves cause an increase of pressure in the ascending aorta in early diastole and not during systole (Figure 1). As a result systolic and pulse pressure is lower in the aorta than in peripheral arteries (Figure 3). Despite these changes of pressure amplitude, mean blood pressure is almost constant throughout the arterial system. The above features are advantageous, since the increase in early diastolic pressure increases coronary perfusion (booster effect) without increasing left ventricular afterload.

Such desirable timing of incident and reflected waves described above can be disrupted (i) when pulse wave velocity is increased due to arterial stiffening, as is seen in uraemia, and (ii) when the 'effective length' of the arterial tree is reduced [1,4,5]. With increased pulse wave velocity the site of reflection comes 'closer' to the ascending aorta and the reflected waves occur earlier, so that they are more closely in phase with

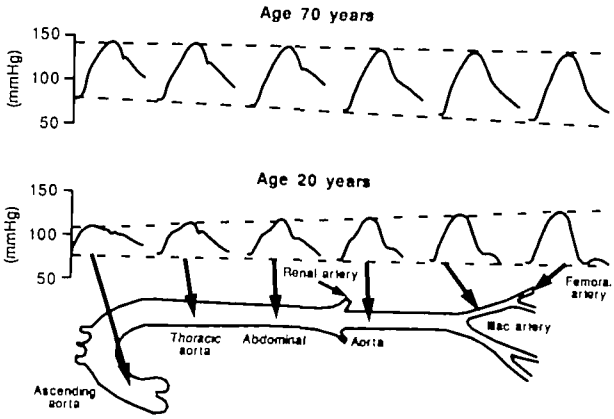

Fig. 3. Pressure waves recorded along the arterial tree in old and young subjects. In the old subject there is little amplification in the pressure wave during transmission, in the young subject the amplitude of the pressure wave increases from the aorta to the peripheral arteries (adapted with permission from Reference 3).

incident waves. The earlier return means that the reflected wave impacts on the central arteries during systole rather than diastole, amplifying aortic and ventricular pressures during systole and reducing aortic pressure during diastole, a finding which is well known in uraemic patients.

The timing of wave reflections in central arteries also depends on the 'effective length' of the arterial tree, which is a function of body height. For any given pulse wave velocity, wave reflections will be relatively delayed in tall subjects and the effect of wave reflection on pressure in the ascending aorta and central arteries will be more marked in short people [4,5].

Why is increased arterial stiffness disadvantageous to left ventricular function? It favours early wave reflection and increases pressure amplitudes. Mean systolic, peak systolic and end-systolic blood pressure are increased in the ascending aorta of individuals with increased arterial stiffness. This will increase myocardial oxygen consumption. At the same time, mean diastolic blood pressure is decreased. This will tend to impair coronary blood supply. Thus coronary perfusion is reduced in the very individual in whom oxygen demand is increased because of increased stroke work. Furthermore, in the long run increased systolic blood pressure induces myocardial hypertrophy, and impairs diastolic left ventricular filling and ventricular ejection. Finally pulse pressure is injurious to the arterial wall. It causes degenerative changes, so that a vicious circle is initiated.

Changes in arterial stiffness and wave reflections with ageing and hypertension

With ageing, stiffness of arteries increases progressively as a result of medial and intimal thickening, accumulation of collagen fibres, deposition of calcium, and degeneration of elastic laminae [3]. The loss of distensibility is partly compensated by progressive arterial dilatation. It is accompanied by a progressive increase in pulse wave velocity [3]. These changes are most marked in the aorta and are attributed to fatigue after decades of cyclic stress. These changes cause a characteristic increase in systolic and pulse pressure. While in the young subject the amplitude of the pressure wave increases from the aorta to the peripheral arteries, amplification is obliterated in the arterial tree of the old subject, because of earlier wave reflection and increased pulse wave velocity. This is explained in Figure 3. Arterial stiffening and early wave reflections contribute to progressive left ventricular hypertrophy in ageing humans. The age-related stiffening of the aortic wall is accelerated in the presence of hypertension [2,3].

In young and middle-aged patients with essential hypertension, increased arteriolar resistance is the principal alteration that causes an increase both in mean blood pressure and in arterial stiffness. It is still not clear whether the stiffening is the passive consequence of an increased mean blood pressure or the consequence of altered arterial wall composition, i.e. smooth muscle hypertrophy and increased collagen content of the media. Systolic hypertension in the elderly is associated with, and presumably results from, intrinsic structural alterations of arterial walls leading to increased arterial stiffness, increased pulse-wave velocity and early wave reflections. Arteriolar resistance may be either increased or normal. Accordingly there may be either (i) systolic and diastolic hypertension or (ii) isolated systolic hypertension with normal or low diastolic pressure.

Arterial stiffness and wave reflections in end-stage renal disease

Why are the above considerations relevant to the clinical nephrologist? Clinical and epidemiological studies have shown a high prevalence of systolic hypertension in end-stage renal disease. According to the EDTA report only 30% of males and 36% of females had a predialysis systolic blood pressure below 140 mmHg, and 32% of both males and females had a predialysis systolic blood pressure over 160 mmHg. This contrasted with a median diastolic blood pressure in both males and females which was in the normal range of 80–89 mmHg [6]. The principal factor responsible for the increased systolic pressure and pulse pressure in such patients is increased arterial stiffness with increased pulse-wave velocity [7,8] and early wave reflections [4,5]. Indeed, arterial stiffness has been shown to be increased in patients with renal failure compared to non-uraemic patients matched for age and mean blood pressure. In this respect, uraemia would be equivalent to primature ageing of the arterial wall.

The mechanisms underlying increased arterial stiffness are not known. The association between decreased arterial distensibility and the presence of arterial calcifications or low HDL-cholesterol levels is weak [7].

These factors therefore do not fully explain the phenomenon. It seems that overhydration, independently from blood pressure changes, directly alters mechanical properties to the arterial wall [9]. The dialysis procedure itself does not improve arterial distensibility [8]. The most obvious consequence of arterial stiffening in uraemic patients is the early return of wave reflections to the aorta and the disappearance of the aortic-to-peripheral pressure amplification [4,5]. This phenomenon occurs prematurely and may already appear during the 4th decade of life in uraemic patients. The early return of wave reflections is an independent factor in the genesis of left ventricular hypertrophy and is also associated with a shorter 'effective length' of the arterial tree [4,5]. This is observed especially in young patients with renal failure and is related to reduced height following growth retardation from azotaemia. Short stature is also associated with increased cardiovascular risk in the general population [10].

Therapeutic implications

If one aims to decrease arterial stiffness in order to delay and reduce wave reflections, one will automatically reduce left ventricular pressure overload. Antihypertensive drugs are certainly beneficial by reducing mean arterial blood pressure. Added benefit will result, however, from concomitant reduction of increased arterial wall tension. Lowering of blood pressure by itself will decrease arterial wall tension, reduce pulse wave velocity, and delay wave reflections.

Beta blocking drugs increase wave reflections and as a result of bradycardia increase the duration of left ventricular ejection, i.e. the time interval available for reflected waves to amplify incident waves [3,11]. For these reasons, beta blockers lower aortic systolic blood pressure less than expected from changes in brachial systolic blood pressure. Drugs that dilate small conduit arteries or which dilate both small arteries and arterioles have a most favourable effect on arterial wave reflections. This is the case for calcium antagonists and angiotensin converting enzyme inhibitors [3]. These drugs will not only decrease mean blood pressure and reduce pulse wave velocity, but will also reduce pulse wave reflection. As a consequence, aortic systolic blood pressure will be reduced more than brachial systolic blood pressure. This may account for the superiority of these drugs in the regression of left ventricular hypertrophy.

It is obvious that obvious cardiovascular management of the uraemic patient entails more than just lowering mean arterial blood pressure. It is hoped that more refined understanding of the above pathomechanisms concerning the circulation of the uraemic patient will also result in more intelligent and targeted interventions. Such an approach will contribute to reduce the appalling cardiovascular mortality of renal patients.

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