Cardiovascular abnormalities in ageing and in uraemia—only analogy or shared pathomechanisms?

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Abstract. The analogies between the effects of ageing and of uraemia on the function and the structure of central elastic arteries and of the heart are striking. Qualitatively similar changes are seen in pulse contour, pulse wave velocity, and impedance and also similar structural abnormalities with wall thickening, diminished elastin, and increased collagen content. The altered ‘Windkessel’ function of central arteries in age and uraemia is one factor contributing to left ventricular hypertrophy.

Introduction

In view of the ageing of the general population, and particularly the ageing of the dialysis population [1,2], it is of considerable interest to examine to what extent in the genesis of cardiovascular end-organ damage the effects of uraemia per se interact with, or are amplified by, the effects of ageing. We select one example which in the past has been underinvestigated, but recently has attracted much attention, i.e. the effect of ageing and of uraemia on the function of, and interaction between, the peripheral vasculature and the heart. Derangements of this relationship are a hallmark of ageing [3], but are also an important aspect of cardiovascular dysfunction in uraemia [4]. In the following, we point out some similarities between the ageing process and uraemia. Based on studies of others and our own investigations [5], we try to provide arguments for the hypothesis [4,6] that the effects of uraemia on the vasculature and the heart can be envisaged partially as the result of accelerated ageing, amplified by the adverse effects of hypertension.

Historical notes

Although investigation of this issue with modern technology has only begun in recent years, it is worth pointing out that the effects of uraemia and ageing on characteristics of the pulse, pulse wave velocity and on the heart had been studied decades ago. In 1872, Mahomed [7] analysed the pulse contour in patients with Bright’s disease and noted a characteristic late systolic shoulder [8], an important observation because this feature will by necessity raise cardiac afterload and contribute to left ventricular (LV) hypertrophy in renal failure.

In a systematic study on the effect of ageing, Bürger in Leipzig analysed the central vessels and heart [9]. He stated that ‘aging changes the chemical composition of the aorta and causes wall thickening’. He further stated that ‘the quantity of elastic elements decreases and consequently the elasticity of the aorta decreases in parallel. This alters the ‘Windkessel’ function, i.e. the dampening of the pulse wave’. He implied that as one grows older, one’s vessels become stiffer. Concerning the impact of ageing on the heart, he noted that ‘with progressive age, the work load of the heart increases. The elastic as well as the peripheral resistances increase progressively. In parallel, increased longitude of central vessels adds to the work load of the central motor. Thus, hypertrophy is truly the result of increased cardiac work load’.

The effects of ageing and uraemia on pulse contour and pulse wave velocity

The methodology to analyse pulse contour and pulse velocity in humans in vivo has been described in detail by O’Rourke [3]. Pulse analysis evaluates pulse amplitude as a function of time, i.e. analysis in the time domain. Ageing is accompanied by characteristic changes of the amplitude and the contour of the pressure wave. Figure 1 paradigmatically illustrates the transitions in amplitude and contour of the pressure wave between the aortic arch and iliac artery of a young as opposed to an elderly human subject [3]. It is obvious that the blood pressure amplitude, i.e. pulse pressure, rises progressively between the ascending aorta and the femoral artery. The peak systolic blood pressure is increased and this is the result of the summation of the incident wave and the reflected wave. An exaggerated systolic peak has been noted not only
in the elderly [10–13], but also in the uraemic individual [4,14–16]. Figure 1 also illustrates that while in the young individual pulse amplitude and contour are markedly different between central and peripheral arteries, this is no longer the case in the elderly. Such a discrepancy of pressure profile between peripheral and central arteries has implications for the definition of hypertension and for the change of cardiac work load with age. In young individuals, systolic blood pressure in the brachial artery, as assessed by sphygmomanometric measurement after Korotkow, is higher than the pressure in the ascending aorta. As age advances, the difference progressively dissipates. It is obvious that the age-dependent increase in pressure in the ascending aorta (and, in parallel, of the left ventricular work load) is greater than the increase in brachial artery pressure. In other words, the increase in the blood pressure load to the heart in the elderly is underestimated based on blood pressure measurements in the brachial artery. In view of the similarities in the biomechanical properties of the central arteries, it is sound to assume that in patients with renal failure the increase is also underestimated. Increasing pulse wave velocity in the elderly has been known for decades [9] (see Figure 2), and this finding recently has been substantiated by modern technology [3]. It is of note that a similar increase in pulse wave velocity is found in uraemia [14,15,17]. This observation raises the issue of whether similar changes in central arterial tissue composition and texture are present in the two conditions.

### The effect of ageing and uraemia on impedance

A type of pulse analysis which is complementary to the analysis in the time domain (see above) is analysis in the frequency domain. For this purpose, the arterial pressure wave is considered as a mean value with fluctuations around this mean. Using Fourier analysis, one can express such fluctuations, as in a musical wave, in terms of component harmonics. The harmonics analysis permits calculation of the impedance, i.e. the relationship between pressure and flow at the input of the vascular bed. A modulus (i.e. ratio of pressure amplitude and flow amplitude) and phase (i.e. delay between pressure and flow as a function of frequency) can be calculated. In the elderly, the ascending aortic flow harmonics are unchanged, while the modulus of aortic impedance is increased. This has important consequences. While under normal circumstances, effective coupling exists between the LV and the systemic circulation, such coupling is progressively lost in the elderly. In the younger individual, the relationship between vascular impedance in the ascending aorta and the frequency content of the LV ejection is such that maximal pulsatile flow from the heart generates minimal pressure fluctuation. As a consequence, minimal energy is lost in pressure and flow pulsations. The

### Table 1. Mechanisms altering vessel wall properties

<table>
<thead>
<tr>
<th>Category</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Physical</td>
<td>Cyclic stretch/fatigue</td>
</tr>
<tr>
<td>Chemical</td>
<td>Advanced glycation end-products (AGES)</td>
</tr>
<tr>
<td></td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>Autacoids/hormones</td>
<td>Renin</td>
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<tr>
<td></td>
<td>Endothelin</td>
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<td></td>
<td>PTH</td>
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Table 2. Aortic cell hypertrophy and hyperplasia and deranged wall matrix composition in subtotally nephrectomized rats

<table>
<thead>
<tr>
<th></th>
<th>Sham operated (n=8)</th>
<th>Subtotal nephrectomy (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>117±9</td>
<td>119±9</td>
</tr>
<tr>
<td>Volume of aortic MC (µm³)</td>
<td>85.5±14.8</td>
<td>97.7±5.8*</td>
</tr>
<tr>
<td>Elastic fibres (%)</td>
<td>63.9±3.9</td>
<td>52.3±2.5*</td>
</tr>
<tr>
<td>Collagen fibres (%)</td>
<td>31.9±4.0</td>
<td>41.4±2.3*</td>
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*Taken from ref. 5.

Unfavourable relationship in the elderly, i.e. unchanged flow into a stiffer tube, causes higher energy loss, increased pulsatile cardiac work and predisposition to LV hypertrophy [3]. It is again of note that recent studies documented uncoupling between the LV and the systemic circulation in renal failure, in striking analogy to the changes seen in ageing [16].

Structural abnormalities of the central arteries in uraemia

Early work of Bürger [9] documented a decrease in elastin and an increase in collagen content in human central arteries. This finding has been confirmed using modern technologies [18]. It appears that the effect of ageing is accelerated by hypertension, at least in experimental studies [19]. The change in viscoelastic properties of the vessel wall with age is presumably explained by physical and chemical factors (Table 1). In engineering, it is well known that cyclic stress causes fatigue fractures. At a heart rate of 60 cycles per minute, 2.4 billion cycles will have occurred during a life span of 75 years. The half-life of vessel wall structural components, particularly of elastin, is in the range of decades. It is therefore no surprise that as age advances, one notes thinning, fraying and fractures of the elastic lamellae in the wall of central arteries. This is accompanied by accumulation of glycosaminoglycans and collagen fibres. As a consequence, arteries dilate, lengthen and stiffen. Because of microfractures of individual elastic fibres, stress is transferred to the less extensible collagen fibres. Since according to Laplace’s law, wall tension in the dilated artery increases, it must be counterbalanced by less structural elements. Consequently, pulsatile stress per unit thickness of fibre increases with age. Against this background, we were interested in the changes that occur in renal failure. In the model of the subtotally nephrectomized male Sprague–Dawley rat, studied after uraemia of 8 weeks duration, the structural features in the aorta were quantitated by micro-morphometric methods [5]. As indicated in Table 2, vascular smooth muscle hyperplasia was documented by increased cell number. Uraemia caused a marked decrease in elastic fibre content and a substantial

Fig. 3. Sham-operated control animal. Normal ultrastructure of the aorta with regular distribution of elastic fibres and regularly sandwiched vascular smooth muscle cells. Ultrathin sections, magnification: 1:10 500.
increase in matrix (and collagen fibre) content of the aortic wall. The reduction in the volume fraction of elastin does not reflect adequately the potential derangement in aortic wall properties, since at the ultrastructural level instead of the regular bedding of elastic fibres, a higgledy piggledy arrangement was noted (Figures 3 and 4). It has been proposed that altered vessel wall properties are related to increased vessel wall calcium content.

In the above study, we did not see evidence of medial calcification, as previously described by Ibeles in humans [20], but it is possible that the duration of experimental uraemia was too short. It is of interest, however, that in muscular and elastic arteries of the subtotally nephrectomized rat, alterations were markedly less in parathyroidectomized uraemic animals, suggesting a permissive effect of parathyroid hormone [21].

Apart from the physical factor of fatigue as a result of cyclic stretch, our unpublished studies suggest that in the aortic wall advanced glycation end-products (AGEs) are present in high concentrations. They cross-link proteins, possibly also the lysine groups of elastin, thus causing vascular stiffening.

It is of interest that according to recent experimental work, oxygen radicals play a definite regulatory role in vascular remodelling. However, pathologically high concentrations, they may cause vascular damage.

Finally, we recently found increased mRNA for renin in the cardiac interstitium [22] and in adventitial tissue of the aorta and conversely, striking prevention of morphological changes in the aortic wall by administration of angiotensin-converting enzyme (ACE) inhibitors [23]. This is illustrated in Figure 5. Furthermore, similar prevention was noted with a specific and non-specific endothelin receptor (ET₄) antagonist (Figure 6). These observations argue for a role of the renin–angiotensin system (RAS) and endothelin systems respectively. The latter finding is in good agreement with recent observations that a relationship exists between biomechanical vascular characteristics and ET-1 levels [24].

Repercussions of abnormal biomechanics of central arteries on the left ventricle

The pulse characteristics are markedly altered in a (hypothetical) uraemic subject compared with a normal individual. In the uraemic individual, peak systolic blood pressure is higher, increasing LV afterload, augmenting LV wall stress and stroke work index and thus contributing to concentric LV hypertrophy. At the same time, the decrease in diastolic aortic pressure is accelerated in the non-compliant stiff aorta of the uraemic patient. Since coronary perfusion
Fig. 5. Effect of ACE inhibitors on aortic wall changes in experimental renal failure. Aortic wall thickness is markedly increased after subtotal nephrectomy (SNX). This increase can be completely prevented by the ACE inhibitor Trandolapril.

Fig. 6. Effect of specific and unspecific endothelin receptor antagonists on aortic wall changes in experimental renal failure. Aortic wall thickening in subtotally nephrectomized rats (SNX) can be partly prevented by the endothelin A receptor blocker BMS 182874 and the unselective endothelin A/B receptor antagonist Ro 46-2005 independently of blood pressure reduction.
occurs only during diastole, this will compromise cor- 

nary blood flow in the heart itself, the oxygen demand of which is high because of increased stroke work. It is therefore logical to postulate that altered biomecha-
nical properties of central arteries are one factor which contributes to the development of LV hypertrophy in the 
ageing individual and in the uraemic individual. Indeed, the LV mass index in uraemic patients is strikingly correlated with age [25], consistent with the hypothesis that there is interaction between the effect of ageing and uraemia. On the other hand, while the effect of uraemia is not pronounced in younger indi-

viduals [26], the effect of uraemia is relatively more pronounced with age, raising the issue of whether the effects of ageing and uraemia are additive or mediated via the same pathways.

The concept of uraemia as accelerated ageing

It is obvious from the above that some analogies exist between ageing and uraemia. The concept does have 

limitations, however.

The vascular wall abnormalities in uraemic patients are reversible, at least partially, after transplantation, as shown by Barenbrock [27]. One would be delighted if similar success could be achieved in reversing the age-induced vascular changes. Second, biomechani-
cal vessel wall characteristics can be altered by medication, for instance ACE inhibitors and calcium channel blockers, and this is also true for uraemic individuals [15,26]. The relative roles played by irreversible structural and reversible functional abnormalities in the genesis of uraemic changes remain unknown.

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