How important and how treatable is vascular stiffness as a cardiovascular risk factor in renal failure?

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Keywords: arterial compliance; arteriosclerosis; cardiovascular mortality; renal failure; vascular function

Introduction

It is possible, with the increasing recognition and repetition of epidemiological data that provide compelling evidence for the appalling toll that cardiovascular (CV) pathology exerts on patients with advanced renal failure, to become both blasé and nihilistic. Dialysis patients aged 20–30 years have the same cardiovascular mortality (CVM) as non-diabetic non-uraemic subjects aged 70–80! Despite the known high prevalence of coronary artery disease in dialysis patients [1], assessment of CV risk relying exclusively on ‘conventional’ CV risk factors incompletely explains these patents’ greatly increased mortality rates. Where Framingham CVM risk scores and actual CV events have been compared (in a renal transplant population) it appears that age, diabetes and smoking seem even more...
Pulse pressure as the most powerful predictor of cardiovascular mortality

While there is no doubt that resistance, muscular (150–400 μm diameter) artery structure and function are abnormal in CRF patients, there has been more research into elastic/large artery structure and function. The majority of HT in CRF, and particularly dialysis, patients is systolic; frequently diastolic blood pressure (DBP) is normal or low [5]. Hence, pulse pressure (PP) is significantly increased. This situation closely resembles isolated systolic hypertension (ISH), typically seen in elderly non-uraemic subjects, but occurring decades earlier in CRF patients. Different anti-hypertensive medications, all of which can reduce blood pressure (BP), can influence PP in different ways [6]. Few clinical trials have deliberately addressed the treatment of ISH (see [7,8] for reviews).

Recent epidemiological studies in the general and hypertensive populations have identified PP as a stronger predictor of future CVM than SBP, which itself is stronger than DBP [9,10]. Very recent evidence has shown this to be the case for haemodialysis patients; Tozawa et al. [11] studied 1243 chronic haemodialysis patients and showed that higher SBP, lower DBP and wider PP all conferred greater CV and total mortality risk. PP was independent of, and more robust than, both SBP and DBP.

Pulse pressure, pulse wave velocity, wave energy reflection and aortic elasticity

PP itself is determined by ventricular ejection (force/time) and by aortic cushioning function. The aorta is of course not only a conduit but also a capacitance device for translating the ‘on-off’ blood flow characteristics of the left ventricle into a smooth non-pulsatile blood flow pattern at capillary level. The degree to which the capacitance function can operate depends on arterial distensibility.

Aortic distensibility (elasticity) determines the degree of energy absorbed by the elastic aorta and its recoil in diastole; the aortic PP in health is modest and lower than peripheral arterial PP. Tempering the rise in aortic SBP protects the distal circulation against barotrauma, and maintaining aortic DBP ensures adequate coronary perfusion. This constitutes perfectly aligned ventriculo-arterial coupling, as seen in young healthy adults. A stiffer, less healthy, aorta begins to fail in both of these tasks.

As well as innate distensibility, there is another phenomenon that impinges on the pulse waveform characteristics: wave energy reflection [12]. Energy propagated down the circulation eventually meets vessel branching points, at which some of the antegrade energy is ‘reflected’ and becomes retrograde. At some point down the aorta the incident and reflected energy waves summate. Where and when this happens depends on the speed of energy transfer along the aortic wall (pulse wave velocity (PWV); see below), on the degree of arterial luminal diameter mismatch (greater mismatch equates to greater reflection) and on the aortic length (closely correlated with subject height). In young, healthy, tall subjects energy summation takes place low in the abdominal aorta, in early diastole, helping to maintain coronary perfusion. Stiffer aortae, with greater pulse wave velocity, constrained aortic branches and a smaller subject height, all combine to cause greater reflection to occur in late systole (rather than diastole as in the healthy state) and with energy summation happening closer to the aortic valve and coronary sinuses, thereby prejudicing coronary perfusion [13].

PP is simple to measure using familiar equipment so it would seem an attractive surrogate measure of aortic stiffness [14]. However, because PP has its origins in both cardiac and aortic performance it is imperfect in this role. Wave reflections can be inferred from detailed computer-aided pulse wave contour analysis. Aortic PWV is a direct measurement of arterial (aortic) stiffness. It is a directly-measured parameter derived from real-time measurement of the time taken for aortic mural energy waves (from cardiac contraction, aortic dilatation then recoil) to propagate down the aorta. PWV is greatly increased in hypertensive and uraemic subjects compared with the general population, and in uraemic subjects it has a much stronger correlation with end-organ damage (LV mass) than does any measurement of peripheral BP [14]. Increased arterial stiffness (increased PWV) is thus mechanistically-linked with systolic HT, widened PP and LVH.

Importantly, both of these facets of arterial dysfunction (greater PWV and also increased wave energy reflection) contribute independently to the increased
end-organ damage, and premature mortality, seen in HT and uraemia.

**How abnormal, large artery structure leads to abnormal arterial function in uraemia**

Large arterial structure is abnormal in CRF and dialysis patients. All arteries are dilated, lengthened and tortuous, but with normal, or even increased, wall thickness. All portions of the arterial wall are involved in structural alterations, which have profound functional consequences. Proliferation of the intima, changes in the media (smooth muscle cell phenotypic alterations, elastic degeneration, reduplication, and cross-linking and calcification) and adventitia (fibrosis) all conspire to ‘stiffen’ arteries; this is most pronounced in the aorta and its major branches [13,14]. Both the degree of large-artery arterial calcification, and the stiffness of the carotid artery wall (elastic incremental modulus), have emerged as the most potent predictors of CVM in French dialysis populations [15,16]. Large- and medium-sized arteries of uraemic patients are simultaneously subject to arteriosclerosis and atherosclerosis (this latter process being accelerated by endothelial cell damage by dyslipidaemia, oxidative stress, homocysteine, ‘micro-inflammation’ and endothelin) [17]. Thus for these structural reasons functional parameters such as PWV [14], augmentation index (pulse wave analysis) [18] and also endothelial vasomotor function [19] are grossly abnormal in dialysis patients.

It should be recognized, however, that quite independently of structural changes there are important changes in arterial function, such as the impact of the accumulation of asymmetric dimethylarginine on endothelial nitric oxide synthase [20].

**Real and potential therapeutic interventions**

While, as with so much in uraemic subjects, prevention is better than a cure, there are several real and theoretical approaches to diminishing, or even reversing, the structural changes that have taken place in the great arteries. Of the various ways that arterial stiffening occurs, it should come as no surprise that the renin-angiotensin-aldosterone axis is highly important. Recent evidence has emerged to suggest that angiotensin converting enzyme inhibitors (ACEI) can ameliorate some of the arteriosclerotic processes in uraemic large arteries, most likely by altering the wave reflectance properties in the major/minor branching points in the distal circulation. Guerin et al.’s study [16] of 150 HD patients whose BPs were monitored and treated vigorously for 51 months showed that in some patients, despite successful BP lowering, the PWV increased. The cohort of patients who had decreases in both PWV and BP showed a marked survival advantage. The use of perindopril (but not nitrendipine or atenolol) was associated with a mortality risk ratio of 0.19 (confidence interval: 0.14–0.43) [16]. Reduction in arterial fibrosis by using ACEI, and spironolactone, has been reported. The thickening/fibrosis of the left ventricle in uraemia happens in parallel with similar mural changes in the large arteries, and both can regress. Nitrates also act to modulate reflected wave energy; eccentric dosing is necessary to prevent vascular tachyphylaxis [21]. The majority of the effects of all of these drugs is not on PWV but more on reducing the extent and altering the timing of wave reflection, leading to reduced ‘late systolic’ augmentation.

It may well be, however, that for many patients on long-term dialysis, vessel structural changes are too extreme to be reversed significantly. Prevention of some of the key processes that promote malign vascular changes must be a priority. Recent reports of agents that can reduce advanced glycation end (AGE) products [22], and more interestingly, prevent collagen and elastin cross-linking [23] in animal models and in man [24], are exciting.

Tackling the vascular calcification (an active regulated process [25,26], when renal patients are so often in a positive calcium and phosphate balance, is much more challenging. Vascular calcification (whether aortic or coronary) has consistently been linked to hyperparathyroidism and vitamin D (ab)use [27], calcium ingestion, and to a ‘closed’ skeleton unable to buffer increases in plasma calcium and phosphate (increasingly the direct result of therapeutic over-suppression of hyperparathyroidism [28]). The adynamic bone syndrome may ironically be of much greater importance to blood vessels than to the skeleton. Raised plasma phosphate in *vitro* has recently been shown to change the phenotype of vessel media smooth muscle cells from contractile to secretory [29], acting as one of a series of triggers that permit true bone formation in the vessel wall. A recent study by Blacher et al. [30] tested the predictive value and independent contribution of large artery vascular calcification (detected by ultrasound) to CVM. They found that the risk of death increased significantly with the number of calcified arterial sites.

Thus, phosphate control is an important ‘cardiovascular’ goal, but avoidance of calcium overload is currently challenging; ironically, we once routinely achieved this using aluminium. The polyallyl compound sevelamer (Renagel; Geltex-Genzyme, Waltham, USA) but not calcium acetate, in the Geltex-Genzyme ‘Treat-to-Goal’ study [31], ameliorated the otherwise relentless progression of coronary artery calcification detected by electron-beam CT scanning. Use of this compound, which also offers significant LDL-cholesterol reduction, gives us some hope that arterial calcification may not be inevitable in everyone, at least in the medium-term. However, the choice of a non-calcium-containing phosphate
The role of renin-angiotensin-aldosterone genetic polymorphisms and the value of quenching excess oxidative stress and inflammation, in order to reduce endothelial damage, through the use of vitamins, folic acid and endothelin-antagonists, urgently need more research. Much more information is also needed about the origins and time-course of these processes. So far, the vast majority of what we know is solely about the origins and time-course of these processes. We must know at what stage in declining renal function these abnormalities begin. If one takes, as one should, the analogy of LVH, these alterations may well start with near-normal renal function.

Effects of renal transplantation on vascular structure and function

We also need to know what happens to large artery structure and function after a successful renal transplantation, and whether any anticipated improvement may explain the reduced CVM in successfully engrafted patients compared with dialysis patients. One would predict that patients transplanted after a relatively short period on dialysis would have the greatest opportunity for vascular improvement. In the era when steroids and cyclosporin A were the dominant immunosuppressives, HT, increased oxidative stress, post-transplantation diabetes mellitus and dyslipidaemia were accepted as necessary evils in the fight to achieve allograft survival, whereas in the modern era, it is both possible and desirable to tailor immunosuppression to the CV, as well as the immunological, risks. Indeed, many different immuno-suppressive regimes can now reduce allograft loss due to acute rejection to <20% in the first post-transplant year. Increasing interest is being shown in steroid avoidance and elimination, and even more attractively, calcineurin-inhibitor elimination, making use of more modern drugs such as rapamycin and mycophenolate. Cyclosporin A in particular has a major negative impact on blood pressure control, oxidative stress and dyslipidaemia [37,38], and, of course, is heavily incriminated in chronic allograft dysfunction. Recent studies have shown that some of its malign influences are wrought by increasing sympathetic nervous traffic, by deranging endothelial function and by increasing arterial stiffness [39,40]; much, if not all of this, is reversible with cyclosporin elimination.

Conclusions

Old-age, diabetes and uraemia share many CV risk factors and pathological mechanisms. These include abnormal autonomic function, vessel dilatation and mural calcification, AGEs and oxidative stress. Increased elastic artery stiffness is also common to all three conditions. We will need to use a variety of agents to counter raised BP, atherosclerosis, calcification and endothelial damage, and the earlier these treatments can be employed the more likely they are to be beneficial.

For now, ACE inhibitors (and most likely angiotensin receptor blockers), nitrates and the avoidance of promoting aggressive vascular calcification are the best remedies we have to ameliorate vascular stiffening. For many patients, however, this is a limited and only partly effective strategy and, thus, vascular stiffening, like LVH, is the norm. The anti-AGE/cross-linking agents require urgent assessment in renal patients, and may prove much more effective.

The traditional reasons why arterial stiffness has been under-valued or ignored, i.e. the relative difficulties of concepts, definitions and measurements, are no longer valid since new apparatus allows rapid examination by the bedside. If prevention of the structural alterations to blood vessels that lead to increased arterial stiffness can be achieved, there is a real prospect of significantly impacting on CVM in dialysis patients. In achieving these objectives we will understand more about some fundamental biological processes, which may have yet more benefits for other diseases.

References


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