Fernando Valderrabano Memorial Lecture

Why is coronary heart disease of uraemic patients so frequent and so devastating?

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On September 6, 2001, Professor Fernando Valderrabano (Hospital Gregorio Marañon, Madrid) died at the age of 59 years. He was a leading figure in Spanish nephrology, a full professor of Medicine/Nephrology at the University Complutense of Madrid, and an outstanding scientist who published more than 300 articles in medical journals. He was a very intelligent and cultured person, and a man of great style who enjoyed a wide range of hobbies and interests in addition to his medical work. All his colleagues and friends mourn his passing.

Background

In 1960 when the sensational news from Seattle, WA, USA, reached the medical community that patients with chronic renal failure can be maintained alive by chronic haemodialysis [1], there was a wide and naive expectation that once uraemia was taken care of, the life expectancy of uraemic patients would be normalized. This complacent view was rudely shocked when Lindner et al. [2] published a landmark paper documenting a very high frequency of coronary heart disease and cardiac death in the first cohort ever of patients dialysed in Seattle. This observation led to the hypothesis of accelerated atherosclerosis in renal failure.

Evidence for accelerated atherosclerosis

The high prevalence of atherosclerotic lesions in uraemic patients has been amply documented by autopsy studies [3,4]. A high frequency of coronary lesions or events has been documented by retrospective and more convincingly by prospective clinical observations [5–9]. But is atherogenesis accelerated or is the high prevalence simply explained by the high frequency of known risk factors?

There are recent tantalizing observations on the very rapid appearance of advanced coronary lesions in young adults with childhood-onset chronic renal failure [10], but overall the clinical observations are not terribly conclusive. We and others therefore resorted to experimental models. Most animal species have high HDL concentrations and do not spontaneously develop atherosclerosis. In the Anitschkov cholesterol feeding model the rabbit will develop atherosclerosis. Indeed, some early work from Denmark [11] showed that rabbits with renal failure develop atherosclerotic plaques in the aorta with some unique properties, but what was really required was a model of spontaneous atherogenesis.

We [12] and others [13,14] investigated the model of the apo-lipoprotein E knock-out (apo-E ko) mouse.
This is an accepted model of spontaneous atherosclerosis and the relevance to uraemia, a state characterized by oxidative stress and generation of advanced glycation end-products (AGE), is obvious. The relevance of this consideration is made even stronger by the observation of Park et al. [15] who injected the extracellular domain of the receptor for AGE (RAGE). This manoeuvre abrogates the interaction of AGE with RAGE, leading to the development of fewer atherosclerotic plaques in diabetic apo-E ko mice.

What happens if one subjects apo-E ko mice to subtotal nephrectomy (Figure 1)? First, one sees larger plaques in the proximal portion of the thoracic aorta (but interestingly not more plaques). This indicates that at least in this model there is no excess de novo development of plaques, but that plaques grow at a faster pace in the proximal part of the aorta. Figure 1 shows plaque diameter (in micrometres) in CB-57 control mice and apo-E-ko mice having been subjected to sham operation, uninephrectomy or subtotal nephrectomy.

The plaques seen after subtotal nephrectomy correspond to soft plaques containing lipid-laden macrophages compared to control apo-E ko mice. The plaques stain more positive for nitrotyrosine (evidence of oxidative stress), for RAGE, i.e. the receptor for AGE (evidence for activation of endothelial cells), osteopontin, collagen IV and others. It is of particular interest that even non-atherosclerotic portions of the intima stain heavily for nitrotyrosine, documenting nitrooxidation of endothelial cell proteins as an early step in the pathogenetic cascade (Figure 2). This is convincing evidence for a role of oxidative stress. We shall come back to the role of oxidative stress, and the potential scavenging of nitric oxide, the vasodilating and vasoprotective compound released from endothelial cells.

It has been increasingly recognized that oxidative stress is important in renal failure, not only for atherogenesis, but also for increased blood pressure. Hasdan et al. [16] and Vaziri et al. [17] found that in uraemic animals, administration of a cell membrane permeant analogue of superoxide dismutase reduces oxygen radicals and lowers blood pressure. Therefore we draw attention to the fact that intra-arterial monitoring of blood pressure even in our atherosclerotic non-uraemic mice clearly documented that blood pressure was significantly elevated.

What is particularly exciting, however, is the observation that in our study, accelerated growth of plaques was seen even when the apo-E ko mice were subjected to uninephrectomy only: fulminant growth of atherosclerotic plaques, as documented in Figure 1.

We conclude first that indeed atherosclerotic plaques grow faster in a uraemic environment and second that this process occurs very early in renal disease. The latter conclusion is in full agreement with clinical observations on intima media thickness or presence of plaques in the carotid artery of patients with only slight elevation of serum creatinine [18,19].
The role of oxidative stress

Oxidative stress, that is the accumulation of such highly reactive oxygen radicals as O$_{2}^{-}$ superoxide, hydroxy radicals, hydroxy peroxide or peroxinitrite can be caused by a number of mechanisms. Reactive oxygen species (ROS) are not necessarily pathological. They are for instance important physiological signalling molecules, mediating the action of agonists such as angiotensin II which stimulates the ROS generating NADP(H) oxidase and triggers a cascade via src, MEK, MAP kinase [20]. Conversely, scavenging of ROS prevents the blood pressure increase and vascular damage after administration of angiotensin II (ANG II), when an excess of ROS occurs, a physiological signalling molecule gone awry, so to speak. ROS interact with nitric oxide (NO) thus generating the highly injurious molecule peroxinitrite. Since angiotensin II is strongly expressed in plaques [21] together with inflammatory cytokines such as IL-6, it will be readily understood why administration of ACE inhibitors as in the HOPE study [22] or of angiotensin receptor blockers as in the LIFE study, reduced cardiovascular events [22,23].

Which reactions cause generation of ROS? As shown in Table 1, their synthesis is promoted by a number of diverse enzymes such as xanthine oxidase in peroxisomes, increased or deranged mitochondrial oxidation via the respiratory chain (which is responsible for hyperglycaemia-induced generation of ROS [24]), NAD(P)H oxidase (for instance after stimulation by ANG II [20]), endothelial nitric oxide synthase in its uncoupled state, for instance when the availability of active biotin is diminished, lipoxygenase or myeloperoxidase, for instance in polymorphonuclear neutrophils (this may be important after contact of PMN with the dialysis membrane). Generation of ROS is further promoted non-enzymatically by transition metals, particularly iron.

When billions of years ago oxygen appeared in the then reducing atmosphere of the earth, most organisms died because oxygen was toxic through generation of ROS. Only few species survived and were ultimately able to harness oxygen for mitochondrial oxidation as an electron donor. As a safeguard against oxygen toxicity, nature had invented a number of protective mechanisms in such organisms which were able to withstand oxygen toxicity (Table 2). These were enzymatic (such as superoxide dismutase or catalase), trace metal scavengers (such as transferrin, ferritin, lactoferrin), and of most interest, non-enzymatic substances such as glutathione or, of interest because of possible therapeutic potential, melatonin, vitamin E, vitamin C, etc. The therapeutic efficacy of vitamin E administration is somewhat controversial [22] despite some recent reports of benefit in a small series of uraemic patients [25], possibly because the isoforms of vitamin E (tocopherol) have widely differing antioxidant potential. Nevertheless, we were recently able to show that administration of high doses of tocopherol to uraemic rats virtually abrogated the morphological abnormalities found in the heart, i.e. interstitial fibrosis, arteriolar thickening and reduction of cardiac vessels of subtotally nephrectomized rats [26].

It follows from the above that an excess occurs when there is an imbalance between the generation of ROS and antioxidant defence. Today there is ample evidence that both pathomechanisms contribute to oxidative stress in renal failure.

Oxidative stress has a number of undesired actions that are relevant in the context of atherogenesis. We restrict these comments to mentioning that amongst others ROS turn on the central inflammatory switch nuclear factor $\kappa$B (NF-$\kappa$B). Normally this pro-inflammatory switch is blocked by the inhibitor I-$\kappa$B. Oxygen radicals abrogate the inhibition and the stimulatory peptides 50 and 65 kDa, translocate then into the nucleus and turn on genetic programmes that cause local or systemic inflammation (Figure 2). This leads to the question: Do we see such inflammation in renal failure?

Witko-Sarsat et al. [27] studied patients in early stages of renal failure. In a certain proportion, increasingly more frequent at higher concentration of S-creatinine, she found elevated plasma concentrations of CRP, interleukin-6 and advanced oxidation protein products (AOPP), IL-1 receptor antagonists and soluble TNF receptors were found. So uraemia per se must be a pro-inflammatory condition, independent of, but aggravated by, dialysis [28]. There is great interest in this field, because recent studies show that CRP concentrations with high sensitivity assays are predictive of overall and specifically cardiovascular mortality not only in the general population [29], but also in the dialysis population [30].

### Table 1. Generation of oxidant species

<table>
<thead>
<tr>
<th>Enzymatic</th>
<th>xanthine oxidase</th>
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<tr>
<td></td>
<td>mitochondrial oxidation</td>
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<td></td>
<td>NAD(P)H oxidase</td>
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<td></td>
<td>endothelial nitric oxide synthase (uncoupled)</td>
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<td></td>
<td>lipo-oxygenase</td>
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<td></td>
<td>myeloperoxidase</td>
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<tr>
<td>Transition metals</td>
<td>Fe$^{2+}$</td>
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### Table 2. Antioxidant defences

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<tr>
<th>Enzymatic</th>
<th>superoxide dismutase</th>
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<tr>
<td></td>
<td>catalase</td>
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<td>glutathione peroxidase</td>
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<td>transferrin</td>
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<td>ferritin</td>
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<td></td>
<td>lactoferrin</td>
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<tr>
<td>Trace metal antagonists</td>
<td>melatonin</td>
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<tr>
<td>Non-enzymatic</td>
<td>tocopherol (vitamin E)</td>
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<td></td>
<td>ascorbic acid (vitamin C)</td>
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<td>carotenoids</td>
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The coronary plaques in the renal and the non-renal patients: the role of hyperphosphataemia

Obviously the frequency of coronary plaques is increased in uraemia, but are there also differences in plaque morphology between uraemic and non-uraemic subjects?

Schwarz et al. [31] found striking differences of coronary plaque morphology when comparing uraemic patients with matched non-uraemic controls. Plaques were categorized according to Stary. There was a striking excess of Stary class 7, that is heavily calcified plaques, which were found four times more frequently in uraemic patients than in controls. In addition the arterial media was thickened, but the coronary lumen area was unchanged, implying that the dreaded inward concentric remodelling of the coronary arteries, which causes coronary artery narrowing and flow restriction, is not a consistent feature of uraemia.

We know from recent exciting findings [32] that what ultimately contributes to the rupture of the plaque is angiogenesis in the adventitial layer of coronary arteries, leading to intramural haematoma formation and rupture of the fibrous cap. We are currently looking into the pathomechanisms in uraemic patients, but the results are not yet definitive.

Together with Professor Altherr (Department of Mineralogy, Heidelberg), sophisticated X-ray diffraction analysis of plaques showed deposition of mature hydroxyapatite crystals. By scanning, we also found deposits of small crystalline granules, few micrometres in diameter in the plaques but not consistently in the media. This differs from that found in muscular arteries [33] and shows that there is a marked heterogeneity between vascular territories. It would not be valid to extrapolate results for instance from the radial artery to the coronary artery.

Naïvely one would assume that calcified plaques are the kind of inert quiescent plaque that one wishes to have. It is now widely recognized that what kills the patient is not so much the plaque causing advanced stenosis, but the non-stenosing, soft, rupture-prone ‘inflammatory’ plaque. This concept may not be universally applicable, however. Although this is still controversial [34,35], model-based calculations point to increased wall stress at the point of transition from the calcified plaque to the adjacent non-atherosclerotic endothelium [35]. This transition zone might rupture for instance when paradoxical vasoconstriction occurs. Atherosclerotic vessel segments are denuded of endothelial cells or are coated by dysfunctional endothelial cells having lost NO-mediated endothelial cell-dependent vasodilatation. They are thus predisposed to paradoxical vasoconstriction. Furthermore, uraemic patients have high sympathetic activity and catecholamine concentrations during dialysis sessions, which reach values seen during a phaeochromocytoma crisis. Both paradoxical vasoconstriction and catecholamine-mediated vasoconstriction may therefore contribute to plaque rupture and cause the malignant character of calcified plaques in uraemia. One cannot exclude, however, that calcified plaques are simply an indicator of a high plaque burden, including both calcified and non-calcified, soft, rupture-prone plaques. This question can only be solved by further investigation.

Recently the issue of coronary plaque calcification in dialysed patients has generated much interest after the introduction of fast imaging techniques that allow detection of coronary calcifications of the beating heart. After the seminal observation of Braun et al. [36], Goodman and co-workers [37] demonstrated a high frequency and rapid progression of calcified plaques in the coronary arteries of adolescents on dialysis. What is still not yet known is whether in dialysed patients the presence of calcified plaques is as predictive of coronary events as it is in non-renal patients.

Risk factor profile in renal patients

Undoubtedly renal patients have a heavy burden of classical coronary risk factors such as hypertension, dyslipidaemia, impaired insulin sensitivity, and endothelial cell dysfunction (the latter presumably resulting from oxidative stress, which is also accompanied by the accumulation of advanced glycation products).

One of the most important issues in this context is the role of dyslipidaemia. Unfortunately, we still lack prospective controlled evidence as to whether interventions with statins confer benefit in the renal patient, although this appears plausible. We currently conduct in Germany the 4D study for which we have completed recruitment of 1200 incident type 2 diabetic patients on dialysis. Patients are randomized to receive placebo or atorvastatin. The results should be out in approximately 2 years time [38]. Numerous interventions are available to deal with other classical risk factors such as blood pressure control, cessation of smoking, or the administration of folate to reduce homocysteine concentrations.

Recently, considerable attention has focused on so-called non-classical risk factors, since many studies showed that the classical risk factors explain only a limited proportion of the variance of cardiovascular mortality in renal patients. We restrict the discussion to two such non-classical risk factors, hyperphosphataemia and elevated concentrations of complement factor D.

Jono et al. [39] noted that in vitro exposure of vascular smooth-muscle cells (VSMC) to high phosphate concentrations changes the VSMC phenotype. Osteoblast-specific molecular genetic programmes are switched on with expression of osteopontin, bone morphogenetic protein isoforms, osteocalcin, Cbfa-1 etc. [40]. This is associated with deposition of membrane-bound hydroxyapatite granules, similar to those we found in plaques, but not convincingly in the media of coronary arteries [31]. This finding is of course of great relevance in view of the observation of...
Coronary heart disease of uraemic patients

Block et al. [41] that in dialysis patients a pre-dialysis serum phosphate concentration of >6.5 mg/dl increases all-cause mortality and specifically the risk of cardiac death [42]. The role of hyperphosphataemia is not restricted to renal patients. Narang et al. [43] found that even in patients with coronary heart disease, but without renal disease, serum phosphate concentration was a potent predictor of the severity of luminal narrowing. This observation may point to a more general role of serum phosphate in the development of coronary plaques. Space does not permit us to dwell on the issue of phosphate binders and the interaction of positive calcium balance with hyperphosphataemia as determinants of the coronary risk.

One further issue has generated remarkably little interest in the renal community, namely the increased concentration of complement (C) factor D of the alternate complement pathway that is observed in uraemic patients [44]. This factor is a low-molecular-weight protein and accumulates in renal failure. Factor D is enzymatically active and continuously cleaves complement factor B, thus activating the alternative C pathway. This has two consequences: it causes a higher rate of spontaneous C activation, so-called tick over of the C system. Furthermore, once the C system is exposed to activating signals, for instance by exposure to bioincompatible membranes, the final readout will be amplified, for instance the concentration of the membrane attack complement C5b9. In other words, the C system of the renal patient is poised to generate higher concentrations of C products and C-dependent injury. This fact is of more than cursory interest. If one analyses coronary plaques by immunohistochemistry, one finds heavy deposits of C in soft plaques. Generally, low concentrations of activated complement cause activation of cells and at high concentrations even necrosis of cells. This is also true for the macrophages in plaques. Furthermore, in coronary plaques complement is co-deposited with C-reactive protein, which is increased in many renal patients as a reflection of the micro-inflammatory state [45]. Co-deposition may indicate co-operation in the generation of tissue damage, but this hypothesis requires confirmation.

Previously we mentioned that oxidative stress is related to micro-inflammation. As a further, not alternative, but complementary, possibility to explain micro-inflammation in renal patients, we propose the intestinal leak hypothesis [46]. In patients with congestive heart failure cardiologists found that oedema of the intestinal mucosa permits permeation of bacterial endotoxin into the systemic circulation. This is accompanied by elevated concentrations of TNF-alpha in the blood. When patients received diuretics and mucosal oedema was reversed, the increase in TNF-alpha was abrogated. We are currently studying whether the same is true in renal patients. The high prevalence of hypercoagulability makes one very suspicious that this may indeed be one correctable co-factor in the genesis of micro-inflammation.

### The cardiovascular risk in the renal patient prior to dialysis

At what point in the evolution of renal disease does the coronary risk increase? The answer is: very early, at a stage when whole kidney glomerular filtration rate is still normal. A normal whole-kidney GFR, for instance measured as inulin clearance, does not of course exclude loss of nephrons. Whole-kidney GFR may not change because of hyperfiltration in residual glomeruli [elevated single-nephron glomerular filtration rate (SNGFR)]. This may explain why Stefanski et al. [47] found a definite increase of blood pressure and an increase in left-ventricular-wall thickness in patients with IgA glomerulonephritis despite a normal inulin clearance. With Fliser et al. [48] we found significant insulin resistance even at a GFR of no less than 80 ml/min. With Kronenberg et al. [49] we showed that proteinuric patients with renal disease may have increased serum Lp(a) concentration even when inulin clearance is still normal, and the same was shown for increased apo-lipoprotein IV concentration [50], which in itself is of course protective. Therefore, this observation merely reflects disturbances of lipoprotein metabolism. Other investigators showed early elevation of homocysteine concentrations [51]. Of particular importance in this context may be the recent observation of Kielstein and co-workers [52] that increased concentrations of asymmetric dimethylarginine (ADMA), an inhibitor of NO synthase, are found in patients with renal disease despite normal inulin clearance. ADMA is highly correlated to cardiac mortality in the general population [53] and in dialysis patients [54]. It is related to carotid intima media thickness [55] and may even be related to coronary events [56]. The reason that ADMA accumulates is not perfectly clear. We found that despite identical molecular weights, the concentrations of the asymmetric (ADMA) and symmetric (SDMA) dimethyl-L-arginine do not change in parallel. SDMA was strictly related to creatinine clearance, but ADMA was not [57]. This observation may point to potential alternative causes of ADMA accumulation in renal failure, for instance diminished enzymatic breakdown in endothelial cells.

### Ischaemia tolerance of the heart

The uraemic patient is not only threatened by coronary plaques per se, but also by the abnormal reaction of the heart to the ensuing cardiac ischaemia. This explains the devastating coronary prognosis of uraemic patients when they develop myocardial infarction as recently shown by Herzog and co-workers [58]. Such excess mortality is not restricted to patients on dialysis; it is seen even in pre-terminal renal failure [59], and may largely explain the excess overall mortality found in patients with elevated serum creatinine [60]. In this context it is of interest that a recent experimental study
showed that coronary ligation causes greater infarct areas in uraemic rats compared to sham-operated control rats [61].

There is a large body of experimental evidence pointing to diminished ischaemia tolerance of the heart in uraemia [62–65]. Because of the potential practical implications, we wish to restrict the discussion to three aspects (i) evidence of micro-vessel disease, (ii) abnormal cardiac metabolism and (iii) sympathetic overactivity.

(i) Micro-vessel disease. Reduced capillary length density has been documented in the hearts of uraemic patients (Figure 3). In other words, the growth of capillaries does not keep pace with the hypertrophy of cardiomyocytes [66]. Because of the mismatch between cardiomyocytes and the capillaries, the distance through which oxygen must diffuse from the capillary lumen to the interior of the cardiomyocyte is increased. This will expose the cardiomyocyte to hypoxia whenever the oxygen supply of the heart is critically low, for instance when coronary blood flow decreases. It could also be shown that the vessel wall of post-coronary arteries within the myocardium is thickened as a result of both hyperplasia and hypertrophy [67]. While this presumably does not interfere with basal blood flow, it will certainly interfere with the vasodilatory reserve that is called upon whenever oxygen demand is increased, a mechanism documented in non-uraemic patients with ‘syndrome X’ [68].

The issue is compounded, however, by a further abnormality. We observed [69] that vascular remodelling is abnormal in uraemia. Vessels adapt to changes in shear stress or wall stress by vascular remodelling, i.e., changes in wall thickening and lumen diameter. This is difficult to study in the beating heart. Therefore we investigated this issue in the mesenteric artery under conditions of controlled high flow and low flow. Particularly under low flow conditions there was striking thickening of the intima (Figure 4), which was accompanied by increased intimal proliferation, as documented by PCNA staining. This abnormality could be abrogated by administering an endothelin receptor antagonist. Intimal hyperproliferation has been well documented in different vascular territories of uraemic patients [7,70] and even in veins not directly used for vascular access [71; our unpublished observations]. We postulate that intimal thickening in low-flow vascular territories would lead to one deleterious
Coronary heart disease of uraemic patients

637

Consequence in the heart: behind a primary coronary artery stenosis, excessive intimal proliferation would cause the appearance of a secondary post-coronary stenosis as a result of post-coronary luminal narrowing. We do not have quantitative confirmation in uraemic patients, but Mall (with whom we collaborate) noted qualitatively narrower lumina in post-coronary myocardial arteries distal to a coronary artery stenosis in uraemic patients compared to non-uraemic patients with coronary heart disease (personal communication).

(ii) Disturbed metabolism of the heart. Raine et al. [62] examined hearts of uraemic rats using NMR spectroscopy in the Langendorf isolated-heart preparation. They showed a decay of energy-rich nucleotides, particularly ATP, and generation of adenosine under low-flow conditions. Furthermore, cytosolic calcium concentration during diastole was increased, raising wall stress and energy demand. Thus, there was a reduction of energy stores, i.e. creatine, phosphate and ATP, together with an increase in energy demand. Our group showed, using the same isolated perfused Langendorf preparation, that insulin-mediated glucose uptake was significantly reduced in uraemic as compared to sham-operated control rats [64] (Figure 5). This abnormality was accompanied by reduced expression of the insulin-sensitive Glut-4 transporter in the myocardial plasma membrane in uraemic animals. Why is this important? Under hypoxic conditions, the heart can no longer generate ATP by mitochondrial oxidation. It is then forced to generate ATP through glycolysis. This reaction requires a large glucose supply, and in the uraemic cardiomyocyte it is this insulin-dependent glucose entry that is compromised.

The potential importance of this issue is illustrated by the recent DIGAMI study, in which it was shown that diabetic patients undergoing myocardial infarction benefit greatly from the administration of insulin and insulin-dependent glucose entry that is compromised. In a recent report from Belgium, diabetic patients undergoing myocardial infarction benefited greatly from the administration of insulin, particularly when they had acute renal failure [73]. This problem should certainly also be studied in renal patients.

(iii) Sympathetic activity. Finally, amongst the factors reducing ischaemia tolerance we emphasize sympathetic overactivity. As described in detail elsewhere [74] chemoreceptors and/or baroreceptors are activated in the damaged kidney, even when GFR is still normal [75]. Activating signals then travel to the hypothalamus where noradrenaline turnover is increased, causing increased sympathetic efferent traffic and increased sympathetic tone. Sympathetic overactivity will increase inotropy and, by implication, oxygen demand. Sympathetic overactivity is the last thing we want to have in a patient with ischaemic heart disease. Unopposed sympathetic activity may be one major explanation for the disastrous outcome of myocardial infarction in uraemic patients [58]. Apart from increasing inotropy, sympathetic overactivity also predisposes to the development of arrhythmia. It is therefore not surprising that in a prospective study, carvedilol was shown to reduce cardiac morbidity and to improve cardiac performance in dialysis patients with impaired cardiac function [76]. Furthermore, in the DOPPS study, only a minority of dialysed patients with coronary artery disease received beta blockers, but mortality in this minority was lower by 13% [77]. It is a pity that for obvious reasons it is extremely difficult to find support for a controlled trial on beta blockers in dialysed patients, but we continue to feel that beta blockers should be much more widely used in the renal patient, whether diabetic or not [78].

Pump failure

The prognosis of advanced heart failure is equal to or worse than that of an advanced carcinoma [79]. It is therefore not completely surprising that in a prospective Canadian study, survival was worst in dialysis patients with systolic dysfunction, i.e. pump failure of the heart [80]. Why is systolic dysfunction so frequent and so devastating in renal patients?

There are numerous abnormalities of cardiomyocyte function in uraemia, e.g. abnormal cardiomyocyte calcium cycling and contractile function [81] and excess sympathetic activity which, in the long run, after an initial phase of increased inotropy, will lead to pump failure as exemplified by the transgenic β-1-adrenergic receptor mouse [82], a model that is pertinent to sympathetic overactivity seen in uraemia [74]. Many novel aspects in the genesis of heart failure have been recently recognized [83,84], but have not yet been adequately explored in renal failure. There has been some progress, however, in one area, i.e. myocyte renewal and ventricular remodelling [85]. In the past it was thought that cardiomyocytes are post-mitotic cells, the number of which remains constant throughout life. Today we know that cardiomyocytes may undergo mitosis and conversely that in the failing heart cardiomyocytes disappear not only by necrosis, but also by apoptosis. It is therefore of interest that recent
work from this laboratory [86] showed that compared to sham-operated rats, the hearts of rats subjected to subtotal nephrectomy contained fewer cardiomyocytes per left ventricle when measured by sensitive stereological methods. This was accompanied by increased apoptosis using TUNEL technique. In other words, one does find cardiomyocyte drop-out in the heart of uraemic animals even in the absence of ischaemia. This abnormality was completely abrogated by the administration of an ACE inhibitor. So not only do renal patients develop more coronary heart disease, but the heart is also more susceptible to ischaemic injury and eventually, amongst other causes, because of cardiomyocyte drop-out it will also more readily develop cardiac failure.

Conclusion

The burden of atherosclerosis is undoubtedly increased in renal failure. Today we have also solid experimental evidence of accelerated atherogenesis. This process starts very early in the development of renal disease. This fact calls for prevention. It also constitutes an important argument that renal patients should be seen by nephrologists early in the course of renal disease.

Apart from classical risk factors, novel uraemia-specific risk factors have been identified, one example being hyperphosphataemia. This has potential therapeutic implications.

A major problem is that the heart in renal failure is more susceptible to ischaemic injury and exhibits ischaemia intolerance because of impaired microvascular adaptation, impaired metabolic adaptation and inappropriately high sympathetic activity. At present atherosclerotic complications, deplorably, still cause high cardiac mortality. We feel, however, that the future is promising because new avenues for therapeutic interventions have become apparent. It would be naïve, however, to assume that a single intervention, a ‘golden bullet’, so to speak, will ever completely eliminate the increased cardiovascular risk. In the future cardiovascular management of the renal patient will continue to remain a complex therapeutic challenge.

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Coronary heart disease of uraemic patients


