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Amann K, Ritz E

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The Heart in Renal Failure: Morphological Changes of the Myocardium – New Insights

K. Amann, E. Ritz¹

In patients with renal failure cardiovascular complications are an important clinical problem and cardiac death is the main cause of death in these patients. It is well documented that cardiac risk is increased by a factor of 20 in uraemic patients compared with age and sex matched segments of the general population.

It has been known for a long time that atherosclerosis, particularly plaques in the epicardial coronary conduit arteries, are more frequent in patients with chronic renal failure. Recently, clinical investigations showed, however, that myocardial infarction is responsible for only 30–50 % of all cardiac death. In contrast, 30–40 % of patients with renal failure and ischaemic heart disease, ie, angina pectoris, show patent coronary arteries on coronary angiogram. Thus, it is very likely that in uraemic patients myocardial ischaemia tolerance is markedly reduced even in the absence of classical atherosclerosis, ie, relevant stenosis of coronary arteries. This finding in patients with renal failure can be at least partially explained by well-described structural and metabolic abnormalities of the myocardium.

The present paper focuses on structural changes of the heart and the vasculature and their potential repercussions for cardiovascular function and in particular their contribution to the high cardiovascular morbidity and mortality in patients with renal failure. *J Clin Basic Cardiol* 2001; 4: 109–113.

Key words: renal failure, heart, left ventricular hypertrophy, myocardial fibrosis, microcirculations

As early as 1827 Richard Bright drew attention to the common presence of left ventricular hypertrophy and thickening of the aortic wall in patients with endstage renal failure [1]. Today, cardiovascular complications are a major clinical problem in uraemic patients accounting for 44 % of all deaths in this population [2]. Death from cardiac causes is 10–20 times more common in patients with renal failure than in matched segments of the general population [3, 4]. Recently, Herzog and co-workers [5] reported that the 1-year mortality rate was 59.3 % in dialysed patients who survived myocardial infarction, ie, mortality was significantly higher than in the general population. Several structural and non-structural alterations of the heart and the vasculature (Table 1) are present in uraemic patients, and they presumably contribute to the increased cardiovascular risk in renal failure. Recent clinical and experimental studies [6, 7, 20–25] clearly document that the pathogenesis of cardiovascular abnormalities in renal fail-

ure is much more complex than initially thought. Apart from elevated blood pressure, hypervolaemia and anaemia, activation of local systems such as the renin-angiotensin system (RAS) and the endothelin (ET) system plays an important role [26–29]. Furthermore, it is widely acknowledged that parathyroid hormone (PTH) is a permissive factor for the development of cardiac and vascular alterations [30, 31]. Whether the rate of development of plaques (atherogenesis) is really accelerated in renal failure as initially postulated by Lindner [32] remains in doubt, but there is no question that there is a very high prevalence of atherosclerotic lesions in renal patients [33]. In the following we shall discuss the issues of left ventricular hypertrophy, coronary heart disease, microvascular disease and cardiac fibrosis. All these structural abnormalities compromise cardiac function. More importantly, they contribute to the increase in cardiovascular mortality that is seen in uraemic patients.

Table 1. Structural and functional changes of the heart in renal failure [6–20]

a) Structural:

- Left ventricular hypertrophy
- Hypertrophy of cardiomyocytes, alterations in myocyte number
- Intermyocytic fibrosis
- Coronary heart disease
- Microvascular disease
 - arteries
 - capillaries

b) Functional:

- Reduction of insulin mediated glucose uptake
- Reduction in the activity of the insulin dependent glucose transporter (Glut 4)
- Reduced stability of energy rich nucleotides
- Abnormal control of intracellular calcium in cardiomyocytes (impaired sarcoplasmic calcium uptake, increased cytosolic calcium concentrations during diastole)
- Reduction of the inotropic and chronotropic response to α -adrenergic stimulation

Left Ventricular Hypertrophy (LVH)

In subtotaly nephrectomized rats [34, 35] as well as in uraemic patients [36] an increase in left ventricular mass is seen very early in the course of renal failure. Stefanski and colleagues examined normotensive patients with biopsy proven IgA-nephritis and normal serum creatinine concentration and found an increase in septal wall thickness and a decrease in left ventricular compliance as reflected by a low E/A ratio [36]. Parfrey et al. [21] found that left ventricular disease was present in 85 % of patients who started dialysis treatment. 16 % of patients had systolic dysfunction, 41 % concentric left ventricular hypertrophy, 28 % left ventricular dilatation and only 16 % had normal cardiac findings on echocardiography. These cardiac abnormalities are closely correlated to the development of heart failure and reduced patient survival. Silverberg et al. noted significantly lower actuarial survival in haemodialysed patients whose left ventricular mass was elevated [37]. By multivariate analysis LVH was an independent predictor of survival. In a non-blinded study Canella et al.

From the Department of Pathology, University of Erlangen, and the ¹Department of Internal Medicine, University of Heidelberg, Germany
Correspondence to: Prof. Dr. Kerstin Amann, Department of Pathology, University of Erlangen, Krankenhausstraße 8–10, D-91054 Erlangen, Germany;
E-mail: kerstin.amann@patho.imed.uni-erlangen.de

documented that left ventricular hypertrophy could be partially reversed by antihypertensive treatment using ACE inhibitors [38]. This was confirmed later in a randomized and double-blind study by London and co-workers [39]. LVH could also be reversed by correction of anaemia with human recombinant erythropoietin (rhEPO) [40–42] and by reduction of pre- and afterload achieved by forced ultrafiltration [43]. In experimental renal failure LVH is associated with an increase in cardiomyocyte diameter and cardiomyocyte volume [44]. These changes lead to an increase in oxygen diffusion distance and must impede diffusion of oxygen to the center of the cardiomyocyte. Apart from cardiomyocyte hypertrophy the left ventricle of uraemic rats has also less cardiomyocytes possibly due to increased apoptosis of cardiomyocytes during the course of renal failure. Based on recent morphologic studies it is questionable whether myocytes are indeed postmitotic cells [45–47]. We found that a certain number of cardiomyocytes in the left ventricle of uraemic rats stained positive for the proliferation marker PCNA (proliferating nuclear antigen); this finding indicates myocyte activation, possibly culminating eventually in apoptosis [48]. Finally, a significant decrease in the number of cardiomyocytes was noted in subtotally nephrectomized rats compared to sham operated controls without signs of cell damage or necrosis [30, 34, 44, 49].

Rambašek et al. [50] found differences in the relative proportion of isomyosins in the hearts of subtotally nephrectomized rats, specifically an increase in the proportion of the fast contracting V₁ fraction with high ATPase activity. This finding is in contrast to what is seen in other forms of cardiac hypertrophy [50].

Using PCR, *in situ* hybridisation and immunohistochemistry we found increased mRNA and protein expression of endothelin 1 (ET-1) in the heart of subtotally nephrectomized rats compared to controls [51]. Using immunohistochemistry expression of ET-1 was also found in the heart of uraemic patients [52]. In addition, left ventricular hypertrophy was found to closely correlate with serum ET-1 concentrations [53].

In experimental animals some LVH could be demonstrated despite interventions to correct anaemia and hypertension [35], but LVH could be prevented, at least in part, by administration of ACE inhibitors, sympatholytic agents, endothelin receptor blockers and rhEPO [8, 42, 51]. Recent experimental studies using the bradykinin receptor blocker

Hoe140 documented that the beneficial effect of ACE-inhibition on LVH is mediated via the bradykinin system [54].

Coronary Heart Disease

Based on postmortem [55] and coronarography studies [56, 57] it is well known that ischaemic heart disease due to stenosis of coronary arteries is very common in patients with renal failure. Apart from sudden death, myocardial infarction is the most common cause of death in these patients. The prevalence of coronary artery stenosis varies from 24 % in young non-diabetic haemodialysis patients [58, 59] to 85 % in elderly uraemic patients (> 45 years) with type I diabetes [60]. Recent findings point to the importance of the morphology of the atherosclerotic plaque: it was shown that the plaque is not a static, but rather dynamic structure undergoing permanent remodeling. Amongst others, the balance between metalloproteinases and tissue inhibitors of metalloproteinase determines stability of the fibrous cap. Plaques covered by a thick fibrous cap are stable lesions, ie, the risk of rupture is relatively small. In contrast, lesions with a large lipid core are unstable and entail a high risk of rupture [61–64]. This concept of plaque stability may explain why only a loose correlation exists between coronary artery stenosis by angiography and cardiac events. It is of interest that in uraemic patients atherosclerotic lesions are far more advanced, ie, more calcified, than in non-renal control patients. Uraemic patients also have a much higher risk of plaque rupture and this may be due to the high density of activated macrophages in the plaques [7, 65]. The intima thickening of coronary arteries of uraemic patients is also increased, consistent with the notion of endothelial cell injury and repair. In addition, overshooting intima proliferation was found under low flow conditions in mesenteric arteries of subtotally nephrectomized rats (SNX) compared to sham operated controls [64].

Microvascular Disease

Intramyocardial Arteries

Confirming previous observations of Roig et al. [67], Rostand and co-workers noted that up to 50 % of uraemic patients with angina pectoris have patent coronary arteries on coronarography [68–73]. This finding is comparable to what was documented in hypertensive patients with syndrome X, ie, angina pectoris despite patent coronary arteries [74]; such

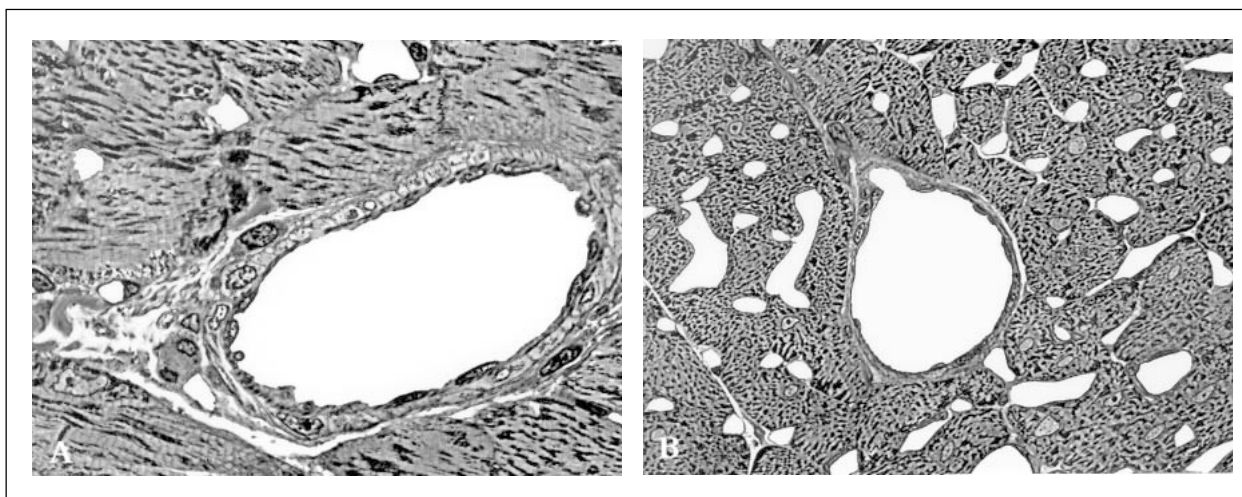


Figure 1. Wall thickening of an intramyocardial arteriole in subtotally nephrectomized rats (A) compared to sham operated rat (B). Semithin sections, mag.: 1:650.

patients have microangiopathy with lesions of the small intramyocardial arteries, ie, wall thickening and reduced arteriolar lumen [75, 76].

In experimental renal failure as well as in uraemic patients wall thickening of intramyocardial arteries is consistently found [7, 77, 78] (Figure 1). The functional consequences of increased arteriolar wall thickness have not been defined. It may not necessarily lead to an increase in baseline vascular resistance, but it may definitely interfere with vasodilatation, ie, with perfusion reserve. Quantitative morphological studies, using unbiased stereological techniques and electron microscopy, documented that the increase in wall thickness is due to an increase in intracellular actin filament content resulting in hypertrophy of arteriolar smooth muscle cells [78]. Immunohistochemical investigations documented increased expression of the vascular endothelial growth factor (VEGF), the platelet derived growth factor (PDGF-AB), collagen IV, actin and integrin- β 1 in the arteriolar wall of intramyocardial arteries in experimental renal failure [48].

Experimental studies clearly documented a permissive role for parathyroid hormone (PTH) in the genesis of wall thickening of intramyocardial arteries [31]. This observation is consistent with several clinical studies showing that PTH concentrations correlate with cardiac morbidity and cardiac death in dialysis patients [79]. Treatment with ACE inhibitors, endothelin receptor blockers, and calcium channel blockers prevented intramyocardial wall thickening after subtotal nephrectomy [8, 51, 80]. This effect of ACE-inhibitors could be dissociated from accumulation of bradykinin [54]. In contrast, non-specific antihypertensive treatment (dihydralazine and furosemide), sympatholytic agents or correction of anaemia with rhEPO did not prevent intramyocardial microarteriopathy [8, 42].

Cardiac Capillaries

In addition to arteriolar changes, reduction of capillary density may further interfere with myocardial blood and oxygen supply. In subtotally nephrectomized rats with moderate renal failure of short [8] and long duration [49], cardiac capillary length density, ie, the total length of all capillaries contained within a unit volume of myocardium, is reduced compared to controls (2485 ± 264 mm/mm³ in SNX vs. 3329 ± 199 mm/mm³ in controls, Figure 2). Such a decrease in myocardial capillary supply was not noted in SHR-SP, an experimental model of essential hypertension. Thus, capillary rare-

faction is specific for uraemia and is not a non-specific consequence of hypertension or LVH. The decrease in capillary density leads to an increase in intercapillary distance [8] potentially compromising blood and oxygen supply of cardiomyocyte under conditions of increased demand. These conditions render the myocardium more susceptible to ischaemic injury.

Similar observations were made in uraemic patients [81]. Reduced cardiac capillary length density was noted in the left ventricles of patients with renal failure as compared to patients with essential hypertension and normotensive control patients. This finding implies that in the LVH of uraemic patients, capillary growth does not keep pace with cardiomyocyte growth, apparently because of some selective inhibition of capillary angiogenesis [81]. The finding of reduced capillary supply is specific for the heart since comparable changes could not be found in skeletal muscle, eg, in psoas [82].

In experimental renal failure, the reduction in cardiac capillary supply could be prevented by the central sympatholytic agent moxonidine [8] and selective and non-selective endothelin receptor blockers [27, 51]. In contrast, treatment with the calcium channel blocker nifedipine, the ACE inhibitor ramipril and correction of anaemia with rhEPO did not affect myocardial capillary density [8, 42]. Treatment of SNX with the bradykinin receptor antagonist Hoe140 resulted in a further decrease of myocardial capillary supply [54].

Intermyocardiocyte Fibrosis

Debove and Letulle were the first to show "that a fibrous growth between the muscular fibres of the left ventricle is common in Bright's disease" [83]. A selective increase in intermyocytic fibrotic tissue was first described by Rössle and Pirani as early as the 1940s [84, 85]. This finding was later confirmed in short- and long-term experimental renal failure [8, 34] and in addition in uraemic patients [81]. A selective increase in cardiac interstitial cell and nuclear volume, but not in endothelial cell volume, was found in association with ultrastructural signs of cell activation [34]. PTH was found to have a permissive effect on interstitial cell activation [30]. PTH and AngII also stimulate cardiac fibroblast proliferation *in vitro* [86]; the stimulatory effect of AngII is potentiated by PTH. Using immunohistochemistry, a significantly increased number of interstitial cells stained positive

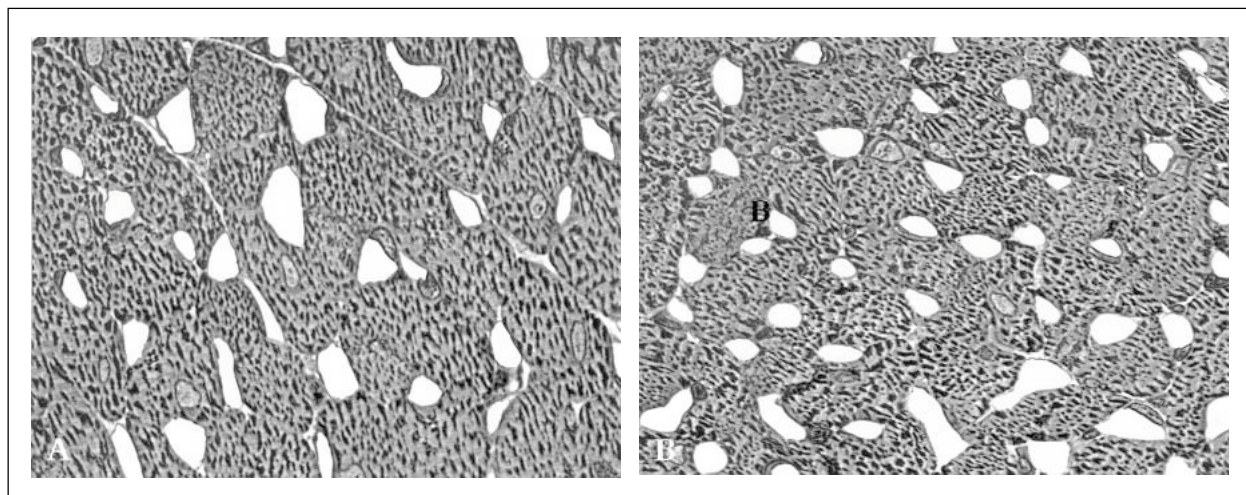


Figure 2. Marked reduction of the number of capillary profiles per area myocardium in subtotally nephrectomized rats (A) compared to sham operated rat (B). Semithin sections, mag.: 1:750.

for the proliferation marker PCNA in subtotally nephrectomized rats compared to controls. In addition, increased expression of PDGF-AB, integrin- β_1 and laminin was found in the cardiac interstitium. This abnormality was not seen in experimental models of genetic and renovascular hypertension or in patients with essential hypertension, respectively, underlining that this finding is specific for uraemia. This is similar to what was noted with respect to the capillary changes. Using non-radioactive *in situ* hybridisation, increased cardiac renin and ET-1 mRNA expression was noted in the cardiac interstitium of subtotally nephrectomized rats compared to controls.

Interstitial fibrosis could be prevented by ACE-inhibition, ET-1 receptor blockade and to some extent also by Ca-channel blockade. The effect of ACE-inhibition is largely bradykinin dependent. Myocardial fibrosis presumably has important functional consequences. Interposition of collagen fibres between cardiomyocytes and capillaries may contribute to myocardial ischaemia by causing displacement of capillaries, reduction of myocardial compliance, changes in the stress-strain-relation and electrical instability by promoting reentrant types of arrhythmias. The latter are thought to be due to fragmentation and local delay of the front of the action potential by interposed collagen fibres, leading to dispersal of the state of refractoriness and favouring reentry tachycardia. This may explain why in patients with essential hypertension cardiac fibrosis is known to be associated with an increased risk of cardiac death due to arrhythmias [87].

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