Morphology of the heart and arteries in renal failure

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Morphology of the heart and arteries in renal failure. In patients with renal failure, cardiovascular complications are a major clinical problem; cardiac death is the main cause of death in these patients. Cardiac risk is increased by a factor of 20 in uremic patients, compared with matched segments of the general population.

It has been known for a long time that atherosclerosis, particularly plaque in the epicardiac coronary conduit arteries, are more frequent in patients with chronic renal failure. Recently, however, clinical studies showed that myocardial infarction is responsible for only 30% to 50% of all cardiac deaths. In contrast, 30% to 40% of patients with renal failure and ischemic heart disease show patent coronary arteries on coronary angiogram. Thus, it is very likely that in uremic patients myocardial ischemia tolerance is markedly reduced even in the absence of classical atherosclerosis (i.e., relevant stenosis of coronary arteries). This finding in uremic patients can be at least partially explained by structural and metabolic abnormalities of the myocardium, and in part by alterations of the extracardiac vasculature. The present paper focuses on structural changes of the heart and the vasculature, in particular on atherosclerosis of cardiac and extracardiac arteries, and its potential repercussions for cardiovascular function.

In 1827 Richard Bright already pointed to the common presence of left ventricular hypertrophy (LVH) and thickening of the aorta in patients with end-stage renal failure (ESRF). At present, cardiovascular complications account for 45% of all deaths in uremic patients [1]. The recent report of Herzog, Ma, and Colins [2] documented a 59.3% 1-year mortality rate in dialyzed patients who survived myocardial infarction (i.e., mortality was significantly higher than in the general population). It is widely acknowledged that several specific structural and nonstructural alterations of the heart and the extracardiac vasculature are present in patients with renal failure, which presumably contribute to the markedly increased cardiovascular risk in these patients [3].

Recent clinical and experimental studies clearly document that the pathogenesis of cardiovascular abnormalities in renal failure is much more complex than initially thought [4]. Apart from elevated blood pressure, hypervolemia, anemia, activation of local endocine systems, such as the renin-angiotensin system (RAS) and the endothelin (ET) system, as well as inadequate activation of the sympathetic nervous system or Ca^{2+} overload, may play a role. Furthermore, parathyroid hormone (PTH) is widely acknowledged as a permissive factor for the development of cardiac hypertrophy, interstitial fibrosis, and arteriolar alterations.

Whether atherogenesis is really accelerated in renal failure as initially described remains a matter of debate, but there is definitely a very high prevalence of atherosclerotic lesions with particularly heavy vascular calcification [5].

The present review shall discuss the issues of LVH, coronary heart disease, microvascular disease, cardiac fibrosis, and extracardiac vascular alterations in renal failure that compromise cardiac and vascular function and contribute to the increased cardiovascular mortality in patients with renal failure.

LEFT VENTRICULAR HYPERTROPHY (LVH)

In subtotally nephrectomized (SNX) rats and in uremic patients, a marked increase in left ventricular mass is seen very early in the course of renal failure. Left ventricular disease is already present in 85% of patients starting dialysis. Sixteen percent of patients had systolic dysfunction, 41% concentric LVH, 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. By multivariate analysis, LVH was found to be an independent predictor of patient survival. Clinically, LVH could be partially reversed by antihypertensive treatment with angiotensin-converting enzyme (ACE) inhibitors, by correction of anemia with human recombinant erythropoietin (rhEPO), and by reduction of pre- and afterload achieved by forced ultrafiltration.

In experimental renal failure, LVH is associated with an increase in cardiomyocyte diameter, which leads to an increase in oxygen diffusion distance and must impede diffusion of oxygen to the cardiomyocyte. Apart from cardiomyocyte hypertrophy, the left ventricle of uremic rats also has less cardiomyocytes due to increased apoptosis during the transition to heart failure. In parallel,

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the development of LVH is associated with a 40% decrease in left ventricular contractility and increased ET-1 mRNA and protein expression. In experimental studies LVH could be prevented, at least in part, by administration of ACE inhibitors, sympatholytic agents, ET-1 receptor blockers, and rhEPO treatment.

CORONARY HEART DISEASE

Postmortem and coronarography studies documented that ischemic 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 nondiabetic hemodialysis patients to 85% in elderly uremic patients with type 1 diabetes. Recent advances in atherosclerotic research point to the importance of the morphology of the atherosclerotic plaque, which was shown to be not a static, but rather a dynamic structure undergoing permanent remodeling. Among others, the balance between metalloproteinases (MMP) and tissue inhibitors of MMP activities determines the stability of the fibrous cap. Plaques covered by a thick fibrous cap are stable lesions (i.e., the risk of rupture is relatively small). In contrast, plaques with a large lipid core are unstable and entail a high risk of rupture. 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 uremic patients atherosclerotic lesions are far more advanced (i.e., more calcified) than in nonrenal patients. Uremic patients also have a much higher risk of plaque rupture, which may be due to the high density of activated macrophages in the plaques [3, 5]. The intima thickness of coronary arteries of uremic patients is also increased, which is consistent with the notion of endothelial cell injury and repair.

MICROVASCULAR DISEASE

Intramyocardial arteries

Previous clinical studies have documented patent coronary arteries on coronarography in up to 50% of uremic patients with angina pectoris. This finding is comparable to what was documented in hypertensive patients with syndrome X (i.e., angina pectoris despite patent coronary arteries); such patients have microangiopathy with plaques of the small intramyocardial arteries (i.e., wall thickening and reduced arteriolar lumen). In experimental renal failure and in uremic patients, intramyocardial arteriolar wall thickening largely independent of blood pressure is consistently found. This may not necessarily lead to increased baseline vascular resistance, but it may interfere with vasodilatation (i.e., perfusion reserve). Quanti-

tative morphologic studies have documented hypertrophy of vascular smooth muscle cells (VSMCs) and increased expression of the vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), collagen IV, actin, and integrin-β1. Experimental studies have clearly documented a permissive role for PTH in the genesis of intramyocardial artery wall thickening; this is consistent with clinical studies showing that PTH concentrations correlate with cardiac morbidity and cardiac death in dialysis patients. Treatment with ACE inhibitors, ET-1 receptor blockers, calcium channel blockers, high doses of vitamin E, or a low-phosphate diet prevented thickening of the intramyocardial arterial wall.

Cardiac capillaries

In addition to intramyocardial arteriolar wall thickening, reduction of capillary density may further interfere with myocardial blood and oxygen supply. In SNX rats with moderate renal failure of short or long duration, cardiac capillary length density (i.e., the total length of all capillaries per volume of myocardium) is reduced compared with controls (−25%). Such a decrease in myocardial capillary supply was not noted in other experimental models with comparable LVH. Thus, capillary rarefaction is specific for uremia and is not a nonspecific consequence of hypertension or LVH. The decrease in capillary density leads to an increase in intercapillary distance (i.e., the distance between the center of a myocyte and the adjacent capillary) and this may further compromise the blood and oxygen supply of cardiomyocytes under conditions of increased demand. These conditions render the myocardium more susceptible to ischemic injury. Similar observations were made in uremic patients. Reduced cardiac capillary length density was noted in patients with renal failure as compared with patients with essential hypertension and normotensive control patients. This finding implies that in LVH of uremic patients, capillary growth does not keep pace with cardiomyocyte growth, apparently because of some selective inhibition or lacking stimulation of capillary angiogenesis.

In experimental renal failure, the reduction in cardiac capillary supply could be prevented by sympatholytic treatment, selective and non-selective ET receptor blockade, as well as antioxidative therapy with vitamin E.

INTERMYOCARDIOCYTE FIBROSIS

Two centuries ago, Debove and Letulle were the first to mention "that a fibrous growth between the muscular fibers of the left ventricle is common in Bright's disease." A selective increase in intermyocytic fibrotic tissue was first described by Rössle and Pirani in the 1940s. This finding was later confirmed in short- and long-term experimental renal failure and in uremic patients [6]. 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. This abnormality was not seen in experimental models of genetic and renovascular hypertension, respectively, or in patients with essential hypertension, underlining that this finding is specific for uremia. Interstitial fibrosis could be prevented by ACE inhibitors, ET-1 receptor blockade, antioxidative treatment with vitamin E and low-phosphate diet.

Myocardial fibrosis presumably has important functional consequences. Interposition of collagen fibers between cardiomyocytes and capillaries may contribute to myocardial ischemia by causing displacement of capillaries, increase in intercapillary diffusion distance, reduction of myocardial compliance, changes in the stress-strain-relation, and electrical instability by promoting reentrant type of arrhythmias. The latter is thought to be due to fragmentation and local delay of the front of the action potential by interposed collagen fibers, leading to dispersal of the state of refractoriness and favoring 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.

CHANGES OF EXTRACARDIAC ARTERIES AND VEINS

In addition to changes in cardiac arteries, patients with renal failure present with thickening of elastic (aorta, carotid artery) and muscular type peripheral arteries and peripheral veins [7]. The increase in aortic wall thickness is primarily due to hyperplasia of VSMCs, but also to an increase in extracellular matrix content with a concomitant decrease and architectural derangement of elastic fibers (Fig. 1). Increased intima-media thickness of the carotid artery and associated alterations of the vessel function in patients with renal failure were shown by Barenbrock et al [8]. Recently, Shoji et al [9] documented that increased intima-media thickness of carotid arteries is already present in patients with renal failure before starting hemodialysis, supporting the concept that the arterial alterations (as well as the cardiac changes) are not due to hemodialysis treatment but to renal failure per se or associated secondary abnormalities.

ATHEROSCLEROSIS OF CARDIAC AND EXTRACARDIAC ARTERIES

The question whether atherosclerosis is more common or more aggressive in patients with renal failure than in matched segments of the general population is hotly debated since the seminal paper of Lindner et al [10], who postulated that "atherosclerosis is accelerated in
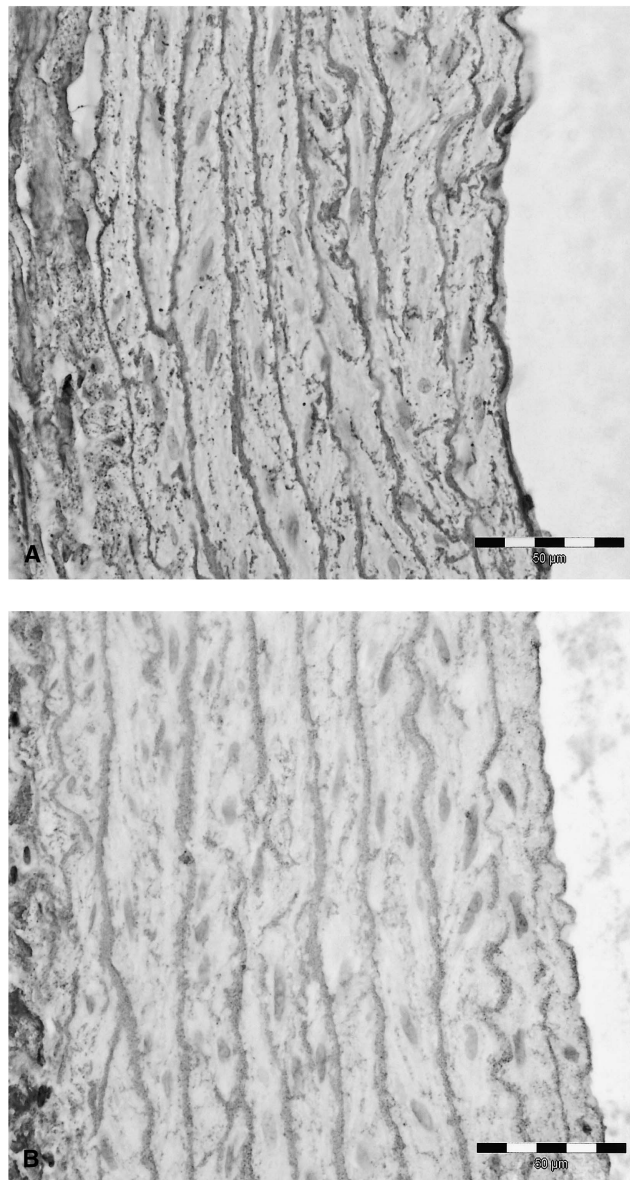
Fig. 1. Aortic wall thickening with changes in the elastic fiber distribution in a subtotally nephrectomized rat (*B*) compared with a control rat (*A*). Paraffin sections, immunohistochemistry.

uremia." Several clinical and, in particular, autoptical studies confirmed the high prevalence of cardiac and vascular calcification in patients with renal failure and particularly in diabetic patients on dialysis [11, 12]. In a recent paper, Oh et al [13] showed that atherosclerosis is even present in very young adults with renal failure. In an autoptical study, plaque composition and size in patients with renal failure was compared with nonrenal patients. Patients with renal insufficiency exhibited more severe lesions and a significantly higher number of STARY type VII lesions, that is, the calcified plaque [5]. Using radiographic diffraction analysis, deposition of hydroxyapatite was confirmed in these calcified plaques, an ob-

servation with potential implications for the clinical management of Ca and P levels. In addition to increased calcification of atherosclerotic plaques, patients with renal failure exhibited marked calcification of the arterial media, particularly in the aorta. This confirms earlier observations of Ibels et al [14], who reported on calcification of the lamina elastica interna, the ground matrix, and of the elastic fibers in patients with ESRF. In recent articles London et al [15, 16] showed that aortic stiffness is an independent predictor of cardiovascular mortality in ESRD and is significantly influenced by medial calcifications. The formation of these microcalcifications can be favored by the above described alterations in elastic fiber content and architecture, as well as derangement in Ca, P, and PTH metabolism.

CONCLUSION

In addition to structural changes of the myocardium and arteriosclerosis of cardiac and extracardiac elastic and muscular arteries and veins, there is now convincing experimental and clinical evidence for the presence of accelerated atherogenesis in patients with renal failure. Atherogenesis starts very early in renal disease and is associated with a high rate of calcification, pointing to a potential pathophysiologic role of nonclassical risk factors such as hyperphosphatemia and hyperparathyroidism [17]. Improvements in the clinical management of these and associated factors could possibly help to reduce the high burden of cardiovascular morbidity and mortality in patients with renal failure.

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