Nephroangiosclerosis and hypertension: things are not as simple as you might think

A. Meyrier, P. Simon

Introduction

The notion that chronic renal vascular lesions proceed from lengthy hypertension or ageing has been universally accepted since their description by Theodor Fahr under the unfortunate term of Nephrosklerose (nephrosclerosis) [1]. Unfortunate, because this word, which means 'renal hardening', stresses but one aspect of the renal lesions, interstitial fibrosis. It overlooks the vascular component, which is rightly found in the European term 'nephroangiosclerosis'. In fact, the German nephrologist followed the lessons of Bright's successors at Guy's Hospital school. The second half of the 19th century had brought two remarkable breakthroughs: the measurement of blood pressure by means of the sphygmograph and the study of human tissues using the microscope. The fact that autopsy of patients who had died with hypertension and renal disease disclosed conspicuous lesions of renal and extrarenal vessels inspired two schools of thought. The first contended that hypertension was the consequence of 'wasting of the kidney'. The other vigorously defended the thesis that the kidney was but one of the organs affected by generalized changes in blood vessels and 'arteriocapillary fibrosis' accompanying essential hypertension. The interested reader will find an excellent review of these disputes in a recent issue of Kidney International [2]. During the 20th century, the concept of 'nephrosclerosis, a consequence of essential hypertension' was more peacefully accepted. The fact that in some individuals, and especially in Blacks of African ancestry, the renal vascular lesions of nephroangiosclerosis can be found at autopsy at a young age [3], presumably before hypertension has set in, did not ruffle this complacency. Moreover, numerous pathological observations of renal vascular lesions in perfectly normotensive persons [4], or in patients suffering from some normotensive form of renal disease, did not kindle particular interest, and it remained the gospel that nephroangiosclerosis is the consequence of hypertension. In fact, things are not as simple as one might think, and we shall present evidence that renal vascular lesions might well be the cause rather than the consequence of essential hypertension.

Terminology is not as simple as you might think

A common error still found in the literature is to neglect the distinction between arterial and arteriolar lesions in the kidney of a hypertensive patient. The specific lesion of nephrosclerosis affects the medium- and small-sized arteries up to the interlobular arteries. Arteriolosclerosis denotes lesions of the afferent and/or the efferent glomerular arterioles which, contrary to arteries, have only one or two layers of smooth muscle cells and no intima or adventitia. Arteriolar lesions are common but not obligatory in nephrosclerosis. They are mainly found in case of malignant hypertension [5], intravascular coagulation [6], ageing [7], and diabetes [8]. In the last, simultaneous involvement of both afferent and efferent arterioles is common. Nephroangiosclerosis is thus essentially a renal arterial lesion.

Renal lesions are not as simple as you might think

The renal lesions of nephroangiosclerosis involve not only the arteries but all the structures of the renal

Correspondence and offprint requests to: Alain Meyrier, Service de Néphrologie et INSERM U 430, Hôpital Broussais, 75014 Paris, France.

Fig. 1. Typical appearance of a renal artery in a case of benign nephroangiosclerosis. This interlobular artery shows intimal thickening by dense collagen tissue. On silver staining (not shown) the elastic laminae are reduplicated. The media is distinctly thicker than normal. The vascular lumen is narrowed. On this preparation the glomeruli appear fairly normal. Conversely, interstitial fibrosis and conspicuous tubular alterations are visible in the renal tissue surrounding the affected artery. (Masson's trichrome, × 250)
Fig. 2. Glomerular retraction and tubulointerstitial lesions in nephroangiosclerosis. Nephroangiosclerosis involves all the structures of the renal tissue. On this figure an ischaemic glomerulus is shown. The tuft is retracted to the hilum, thus widening the urinary chamber. Bowman's capsule is thicker than normal. Greater magnification with silver staining would show that the glomerular basement membranes are folded. Note the tubulointerstitial lesions in the adjacent area. (Mason’s trichrome, ×250)

Fig. 3. The decline in renal function of nephroangiosclerosis also proceeds from extravascular lesions. This is illustrated on this picture. Large hyaline deposits are still visible in a glomerulus, which appears virtually obsolescent. Such scarring might be the consequence of overlooked episodes of malignant hypertension accompanied with bouts of intravascular coagulation in the course of the disease. The interstitium is interspersed with several foci of fibrosis. Tubular alterations are severe. The tubules are atrophic and microcystic. They contain hyaline casts giving the classical appearance of 'pseudothyroid areas'. (Mason’s trichrome, ×250)

Pathophysiology is not as simple as you might think

Nephrosclerosis has long been considered the consequence of high blood pressure or of ageing. That tissue [5]. The arcuate and interlobular arteries show myointimal hypertrophy, reduplication of the internal elastic lamina and hypertrophy of the media. The arterial wall is thickened by hyaline, eosinophilic, PAS-positive deposits, and the smooth muscle cells are atrophic. The vascular lumen is narrowed. Along with arterial changes, glomeruli are usually ischaemic, with thickened and folded capillary walls. Numerous glomeruli are completely sclerotic. The renal tubules are also atrophic, with thick basement membranes, and contain protein casts. Finally, extensive interstitial fibrosis contains inflammatory cells. In many cases the appearance of renal biopsy resembles that of chronic interstitial nephritis. In case of aortorenal atheromatous disease, cholesterol crystals may occasionally be found in medium-sized vessels and even within some afferent arterioles.

By definition, the diagnosis of nephroangiosclerosis can only rest on histology. A common error in countries where renal specialists are reluctant to carry out renal biopsy is to consider that a middle-aged or elderly patient with renal insufficiency, no evident disease other than primary hypertension, normal urinary sediment, and slight or microalbuminuria suffers from nephrosclerosis [9,10]. This laxity was rightly criticized by Zucchelli and Zuccala [11]. In 136 patients diagnosed as having 'benign nephrosclerosis' thorough diagnostic workup, including renal biopsy, disclosed cholesterol emboli in 29.4%, renovascular disease in 26.5% and true nephrosclerosis in only 44.1%. In the United States, Schlessinger et al. [12] reached similar conclusions concerning the propensity to wrongly label similar patients as suffering from 'nephrosclerosis' in the absence of renal biopsy.

Pathophysiology is not as simple as you might think

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Some three decades ago, in the description of Bartter's syndrome. Chronic diarrhoea and hypertension. More recent experiments shed entirely new light on the relationships between nephrosclerosis and hypertension. They seriously disturb the conventional concept that when nephroangiosclerosis is found on biopsy, primary hypertension is the villain and renal arteries the victim. In 1988 Smeda et al. [26, 27] treated...
spontaneously hypertensive pregnant rats with hydralazine. Their offspring were normotensive at birth and yet exhibited thickening of renal vascular walls. The authors raised the provocative hypothesis that genetic nephrosclerosis might well be the cause rather than the consequence of hypertension. In mice rendered hypertensive by knock-out mutation of the ACE gene, renal histology showed thickened and hypercellular renal vascular walls [28]. Genetic manipulations can yield mice with zero to four functional copies of the angiotensinogen gene. The former are hypertensive, the latter hypotensive. Which do you think exhibit the most severe renal vascular lesions? The right answer is not as simple as you might think: Kim et al. [29] found the most severe lesions in the hypotensive mice. In the same line, a nil mutation of the angiotensinogen gene yields a homozygous hypertensive strain of mice [30]. As of the third week of life their renal cortical vessels display lesions of nephrosclerosis along with hyperexpression of PDGF-B mRNA and TGF-β1. In these angiotensinogen-deficient mice, intrarenal renin levels are very high. Taken together, these findings lead to the exciting hypothesis that renin rather than angiotensin exerts a significant influence upon vascular cell proliferation.

Treatment is not as simple as you might think

That treatment of hypertension is probably the most convincingly proven element in slowing the pace of chronic renal disease, be it secondary to some form of nephropathy or to primary hypertension, has been amply demonstrated [31]. The benefit of lowering blood pressure levels is not disputable. However, on the basis of experimental data concerning the favourable effect of angiotensin II inhibitors upon smooth vascular cell proliferation and arterial wall collagen build up, it has been contended that ACE inhibitors are superior to other antihypertensive agents in protecting the kidney from development of nephrosclerosis. Some investigators, studying a series of patients with long-standing hypertension and microalbuminuria, considered this combination as sufficient argument to pose a diagnosis of nephrosclerosis in the absence of renal histology. Finding that ACE inhibitors had reduced or suppressed microalbuminuria, they drew the hasty conclusion that ACE inhibitors protect the kidney from the deleterious effects of angiotensin II [32]. Very few experimental or clinical data are available to prove or disprove this view. We would like to propose two publications for the reader’s reflection. The first is the experimental work by Michel et al. [33], who induced unilateral renal ischemia in rats and treated these hypertensive animals with an ACE-inhibitor. At histology, the stenotic kidney showed increased, not improved, ischaemic lesions. More recently Acone et al. [34] analysed the effect of blood pressure control on the progression of renal failure in elderly patients with chronic renal disease. Twenty two were diagnosed as hypertensive nephropathy. One group was treated with calcium antagonists and another with an ACE inhibitor. In the latter the decline in renal function was significantly more rapid than in the former.

In conclusion, the conventional notion that primary hypertension is the principal cause of nephrosclerosis calls for thoughtful, and even painful reconsideration. Nephrosclerosis might well be a primary genetic renal vascular disease leading to hypertension. Renin, rather than the passive substrate of angiotensin II generation, might have its own specific role in the development of the renal vascular system in the embryo, but also a deleterious effect on the renal vasculature of the mature kidney. ACE inhibitors might transpire, in the long run, to be less the miracle vaccine against nephrosclerosis than has been proclaimed over the last decade.

With regard to nephrosclerosis and hypertension, things are not as simple as you might think, and future clinical and experimental studies could lead to seriously reconsidering the aetiology of nephroangiosclerosis.

References

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**Heparin-induced thrombocytopenia—background and implications for haemodialysis**

G. Finazzi and G. Remuzzi

1. Mario Negri Institute for Pharmacological Research, Bergamo; 2Division of Hematology and 3Division of Nephrology and Dialysis, Azienda Ospedaliera, Ospedali Riuniti di Bergamo, Bergamo, Italy

**Background**

Heparin-induced thrombocytopenia (HIT) is a well-recognized complication of heparin therapy, frequently associated with severe thrombotic events. The reported frequency of HIT varies widely. Cumulative data from literature suggest a prevalence of about 5% in patients receiving unfractionated heparin and a significantly lower rate in subjects treated with low-molecular-weight heparin (LMWH). In a recent study HIT occurred in 9 of 332 patients who received unfractionated heparin and in none of 333 patients who received LMWH as prophylaxis after hip surgery (2.7 versus 0%; \( P = 0.0018 \)) [1]. Typically, HIT appears after 5–8 days of therapy, but it can occur sooner in patients previously treated with heparin. In most patients, platelet count falls below 50,000/μl, but thrombocytopenia in itself rarely poses a clinical problem because bleeding symptoms are unusual. On the contrary, patients with HIT may develop life-threatening vascular occlusions, including venous thromboembolism, cerebral thrombosis, myocardial infarction, peripheral arterial thrombosis, and disseminated intravascular coagulation.

An immunological mechanism leading to HIT and thrombosis has been recently postulated [2]. The key event is the formation of a ternary immune complex between IgG, heparin and platelet factor 4 (PF4), a heparin-binding protein derived from alpha granules. The immune complexes bind to Fc receptors of circulating platelets inducing platelet activation and additional release of PF4. In the presence of heparin, more immune complexes are formed and a cycle of platelet activation and consumption is established. In addition,