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THE DILEMMA OF RENAL FAILURE DUE TO HYPERTENSION

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Summary. *The data provided by the End-Stage Renal Disease (ESRD) Registries documenting a progressive and striking increment over the years of the Hypertension-related ESRD incidence and prevalence support the classic statement that the kidney may be a victim of hypertension. Long-lasting hypertension may induce ESRD in a few patients throught hypertensive nephrosclerosis, particulary in African-Americans. In many cases of progressive renal disease associated to essential hypertension, particularly in elderly Caucasians, atheromatous renovascular disease via renal artery stenosis and/or cholesterol microembolization represent an important cause of ESRD.*

Key words: *Hypertensive nephrosclerosis, renal artery stenosis, cholesterol microembolization*

Introduction

Arterial hypertension represents a major public health problem in the Western Societies for its high frequency among the unselected population and, particurarly, for its strong association with cardiovascular morbidity and mortality. Progressive renal disease has always been comprised among the possible end-organ damage-related to hypertension (1). This topic of hypertension and renal injury has received growing interest in the last decade mostly due to the data offered by the End-Stage Renal Disease (ESRD) Registries (2). In fact, hypertension as a cause of ESRD has risen progressively and more rapidly than all other causes (except diabetes mellitus) in North America and Europe. Hypertension-related ESRD currently accounts for 29% of the newly treated patients in the USA (38% of African-Americans and 25% of white Americans) while it is 21% in France and 27% in Italy (2,3). As the number of patients with malignant hypertension has dramatically decreased over the past two decades, it follows that mild-to-moderate essential hypertension, which is the almost totality of hypertensive patients, may play an important role in the genesis of progressive renal insufficiency (4,5). However, there are at least two contradictory aspects that constitute the dilemma of hypertension induced renal insufficiency: 1) the paradoxically relentless increase in hypertensive ESRD rates is associated with a significant reduction of morbidity and mortality from stroke and coronary artery disease as a result of a widespread and effective antihypertensive treatment (6); 2) the causative role of essential hypertension for ESRD has been questioned, if not refuted, by many Authors due to the contrasting experimental, morphological, and, particularly, epidemiological observations. This later aspect needs a longer discussion (4,5,7,8).

Hypertension and renal failure

Epidemiological data on the risk of hypertensive patients to develop renal failure offer contrasting results. In the Baltimore Longitudinal Study of Aging, white-middle class hypertensive patients lost renal function at a faster rate with aging than normotensive subjects. However, the rate of decline was very small and unlikely to result in ESRD (9). Furthermore, Rosansky et al (10) in a retrospective study of essential hypertensives followed up for a mean period of 9.8 years found a greater rate of change in serum creatinine over time in hypertensives than in controls but with no statistical significance; the difference was marked for black patients. In addition, autopsy studies on patients with pure essential hypertension suggest that severe renal damage consequent to high blood pressure, in the absence of associated renal parenchymal disease, is either rare or non-existent (11).

Another point that emerges from longitudinal studies is the different behaviour of renal function in blacks compared to whites. Tierney et al (12) have analyzed data from 6,880 hypertensive patients followed up for several years. An abnormal final serum creatinine value (2 mg/dl) was found in 18.1%. Indicators of decreased renal function were systolic blood pressure, diabetes mellitus, heart failure, male gender and black race. In addition, Rostand et al. (13) documented a frequency of 15% of renal function loss among their essential hypertension patients, the majority African-Americans,

with no difference between good or bad pressure control. Lastly, in the Multiple Risk Factor Intervention Trial (MRFIT), 5.6% of 5.524 hypertensive subjects had a negative slope of serum creatinine over time. The rate of decline in renal function was greater in older individuals, in blacks, and in those with higher systolic blood pressure (14). Other studies have analyzed the impact of antihypertensive therapy on renal function. In a review performed by Whelton and Klag (15) of the six major antihypertensive treatment trials with over 20,000 patients-years of follow-up, the total number of renal events was very small, with no difference between the active and placebo grupus. In the European Working Party on high blood pressure in the elderly trial, a randomized, double-blind, placebo-controlled study of the effects of antihypertensive therapy on morbidity and mortality in hypertensives over the age of 60 (16), the impact of hypertension on renal function was also examined. Overall, the treated group did less well as regards renal function and the Authors concluded that renal insufficiency rarely occurs in the elderly hypertensive. In the Multiple Risk Factor Intervention Trial (14) the cohort of men with mild-to-moderate hypertension was randomized to a special intervention group that underwent an aggressive, four-step, anti-hypertensive treatment, or to a usual care group in whom the standard treatment was maintained. Although the special intervention group had a better control of blood pressure than the usual care group, no difference between the two groups was observed in the reciprocal serum creatinine slopes. The inability of anti-hypertensive therapy to influence kidney destiny emerges also from the recent work by Madhavan et al (17) is which no correlation was found between blood pressure responses to anti-hypertensive therapy and the course of renal function in patients with mild-to-moderate hypertension followed-up for five years. Only in black patients, strict blood pressure control seems to be able to block renal disease progression (18). On the whole, the role of hypertension as the only etiologic factor leading to renal failure seems to be sufficiently clear in African-Americans. Hypertension is more common, more severe and less well managed in the black compared to the white US population. This fact, possibly associated to a different renal architecture and/or renal circulation, as well as a hyperresponsive vascular smooth muscle cell to growth factors may explain the significantly greater incidence of hypertension-related ESRD in this racial group (19,20). On the other hand, the claim that primary hypertension per se may be a frequent cause of renal failure in Caucasians does not seem to be confirmed by the clinical and epidemiological data. A possible explanation for the discrepances between the high prevalence of ESRD classified as due to hypertension-induced nephropathy and the above-cited epidemiological data may be the widespread use of the term hypertensive nephro(angio)sclerosis. Moreover, in many countries, the same code is used, for hypertensive nephrosclerosis and renal vascular diseases such as atherosclerotic occlusive disease, major renal vascular disease, and atheroembolic issue (so called "ischemic nephropathies"). Some recent studies have clearly documented that renal insufficiency associated to essential hypertension comprises many disease processes as listed in table 1.

Table 1. Renal insufficiency associated to hypertension

Malignant hypertension
Undiagnoses primary renal disease
Hypertensive nephrosclerosis
Ischemic nephropathies:
a) renal artery stenosis
b) cholesterol microembolization
c) antiphospholipid syndrome

Hypertensive nephrosclerosis (or nefroangiosclerosis)

The kidneys of essential hypertensives studied at autopsy or by renal biopsy show vascular abnormalities characterized by arteriolar hyalinosis (predominantly at the afferent glomerular arterioles) associated with subendothelial and medial fibrosis in the interlobular and large arcuate arteries. Focal tubular atrophy and interstitial fibrosis of various entity with obsolent or ischemic glomeruli predominantly in the juxtamedullary areas, is a constant feature, sometimes with focal and segmental sclerosis and hyalinosis (21,22). Nephroscle-rosis is essentially a renal histological lesion but not specific of hypertension because age may induce similar renal abnormalities (23). The mechanism by which the elevated blood pressure can induce pregressive renal failure is not clearly known. Two different hypotheses have been put forward: renal damage is the result of glomerular ischemia and hypoperfusion due to the narrowing of preglomerular vessels, as it happens in severe renal artery stenosis; or it's the consequence of glomerular capillary hypertension and hyperperfusion due to a loss of the renal autoregulatory response normally presence also in the early phase of essential hypertension (24).

Can be hypertensive nephrosclerosis responsible for progressive renal disease and ESRD?

Undoubtdly yes in African Americans as it was very recently shown in a pilot study of the African American Study of Kidney Disease (ASSK) Trial. Among 39 patients with mil-to-moderate renal insuficiency who were submitted to renal biopsy the great majority showed renal vascular lesions consistent with the clinical diagnosis of hypertensive nephrosclerosis. Interestingly, cholesterol emboli was found in two cases

(25). These data further stressed the importance of black race in the appearance of hypertension-related ESRD confirming the presence of an inherited defect in the control of the renal circulation in these patients.

In Caucasians, hypertensive nephrosclerosis may be or is the cause of ESRD but in a small fraction of ESRD patients. In fact, Innes et al, by using the UK Medical Research Council (MRC) glomerulonephritis Registry (26), have classified the 2.5% of renal biopsies, among 7,339 biopsies in hypertensive patients with renal insufficiency and proteinuria, solely as benign hypertensive nephrosclerosis. In 1991 we performed a retrospective study on 136 patients diagnosed as having hypertensive nephroslcerosis on clinical basis according the following criteria: a history of prolonged hypertension in a patient with low-grade proteinuria, and grade I or II retinopathy (according Keigh-Wegener classification), small and scarred kidneys, and no evidence of primary renal disease (27). A thorough diagnostic workup, including renal biopsy, disclosed true nephrosclerosis in 44.1% of the cases. Finally a prospective study of our performed subsequently in 58 patients having the clinical characteristics previously described offered data summarized in Table 2.

Table 2. Final diagnosis of 58 consecutive patients clinically considered as having hypertensive nephrosclerosis

Final diagnosis	No of patients
Analgesic nephropathy	1
Unsuspected IgA nephropathy	1
Immunotactoid nephropathy	1
Light-chain deposition disease without free light chains in the plasma and urine	1
Unclassified	8
Atheromatous renovascular disease	19
True hypertensive nephrosclerosis	27

At present we cannot say who are the benign essential hypertensives at risk of developing renal insufficiency: those showing microalbuminuria, or salt-sensitive patients, or those having some genetic phenotype or finally, those in whom high blood pressure values were not constabtly controlled, or in whom dyslipidemia, insulin resistance, hyperuricemia, alterations in immune function coexist with hypertension?

Atheromatous renovascular disease

In our experience, many cases of so-called hypertension related ESRD represent the consequence of atheromatous renovascular disease (Table 2). In other words, progressive renal disease associated to hypertension, at least in aged Caucasians, is frequently the consequence of atherosclerosis more than of the elevated blood pressure.

Over the past decade, renal atheromatous disease has been the subject of intensive work (23,28,29). It may cause progressive renal insufficiency either by causing renal artery stenosis (RAS) or by being the source of renal cholesterol embolization. As atherosclerosis RAS is common in patients with generalized atherosclerosis, the two processes may frequently coexist in the same patients.

The incidence of critical renal artery stenosis in the unselected population is not known but at least 3 autopsy studies (cited in n 30) suggest that significant atherosclerotic disease of the renal artery has a very high prevalence in older ages of the white population, varying from 4.3 to 18% of patients between 65 and 74 years, and 42% of patients of 75 years of age. The stenosis was bilateral in 30-50% of the patients. In addition, the presence of RAS has been estimated by renal angiography during evaluation of extrarenal atherosclerotic vascular disease. On the whole, these angiographic studies demonstrate the presence of a significant RAS in about a third of around 2,500 patients, almost always Caucasian, over 50 years of age. Unsuspected renal artery stenosis is also commonly found in patients with coronary artery disease. At least 5 studies in around 2,300 patients undergoing cardiac catheterization had significant RAS in up to 25% of them (30,31). In addition several studies (23,28,29) have clearly documented that atherosclerotic RAS may be progressive in many patients as listed in table 3.

Although the above cited data should be interpreted with caution for their retrospective nature, they suggest that approximatelyy half of the involved patients has progressive disease ending up with complete artery occlusion.

Table 3. Serial angiographic studies

	Patients	Progression	
		N	%
Dustan et al, 1966	18	11	61,0
Wollenweber et al, 1968	30	21	70,0
Dean et al, 1981	35	10	28,5
Schreiber et al, 1984	85	37	43,5
Zucchelli et al, 1987	24	9	37,5
Tollefson and Ernest, 1991	48	34	70,8

Renal artery occlusion, frequently unilateral, associated to chronic reduction of blood flow to the other kidney induces significant changes causing tubular atrophy and dilatation with profound alterations of the antigenic profile of the proximal tubules responsible for progressive chronic interstitial fibrosis (32) that may cause progressive renal insufficiency in a substantial portion of patients. Many data in fact documented that ischemic nephropathy accounts for 5 to 22% of all patients developing ESRD each year in the Western World. The large majority of such patients are elderly, Caucasians, hypertensive, frequently heavy smokers, with generalized atherosclerosis (30,31).

If ischemic nephropathy represents an important problem, are we equipped to cope with this threatering

problem? Clinicians dealing with this disease face three different problems:

- Choosing the diagnostic examination offering the greatest advantage at the lower cost: in our hands Duplex scanning and spiral CT - angiography represent our preferred tools (33,34).
- Chooosing between the revascularization and the conservative approaches. This point is a very critical, in fact, numerous reports in the literature suggest the advantage of renal renovascularization in retriering and/or preserving renal function (35). Unfortunately, there is no prospective, controlled study that verified the superiority of revascularization as against a more conservative approach (medical therapy). Therefore, no guideline can be properly proposed and only personal jugdment and experience can be used. Due to these doubts the thirst problem, i.e.
- Choosing the type of intervention, i.e., renal angioplasty, stent, surgery can only be advised on a personal experience.

In conclusion, ischemic nephropathy is and will be in future an increasingly formidable challenge for nephrologists and only in the future we nurture the reasonable hope of successfully facing up to the looming threat because our diagnostic and therapeutic tools are continuously improving.

The problem of atheromatous renovascular disease is more and more complicated by the frequent association with cholesterol crystal embolization. Cholesterol microemboli, released from ulcerated or fractured atheromatous plaques in the aorta and/or major arteries, is a frequent autoptic finding in patients with advanced atherosclerosis. In fact, in various autopsy series it frequency has varied from 0.79 to 17% (36). Over the last decade renal atheroembolism has become a growing cause of renal problems even though the diagnosis is frequently missed.

Two major forms are clinically present: an acute or subacute scenario usually following invasive procedures (angiography, cardiovascular surgery, etc) or during anticoagulant therapy. In atheromatous RAS cholesterol microembolization into the kidney may complicate the disease as it may happen spontaneously or following diagnostic and therapeutic procedures. The appearance of progressive renal failure after some weeks of the procedure associated with non renal manifestations (livedo reticularis, purple toe, amaurosis fugax, and so on) may point to the diagnosis.

In addition an indolent form i.e. the appearance (or worsening) of renal insufficiency in patients with long-lasting hypertension may be confused with hypertensive nephrosclerosis unless a renal biopsy is performed. Interestingly, in the AASK cited before (25), two cases of cholesterol microembolization are reported on 39 African-Americans. In our study on 58 consecutive patients, 6 out of the 19 patients with atheromatous renovascular disease had cholesterol microembolization.

The presence of severe atherosclerosis with on without aortic aneurism in a male aged Caucasian may point to the clinical diagnosis. In a recent study, Mayo and Swartz (37) reviewing 402 consultation charts in a large academic institution, stated that cholesterol microembolization appeared at a rate of at least one every two weeks.

Conclusions

Many data suggest that there is a striking racial difference in hypertension-related progressive renal disease. Hypertension is certainly more common, more severe, less well managed, and more capable of causing renal insufficiency in African-Americans compared to whites. The mechanisms responsible for such a renal susceptibility are still unknown.

In Caucasians, progressive renal disease may appear especially in elderly patients with essential hypertension. In many cases, the appearance of renal insufficiency, often despite adequate blood pressure control, is frequently associated with atheromatous disease of the aorta and/or renal arteries. Atheromatous renovascular disease may cause progressive renal insufficiency through renal artery stenosis and/or chronic cholesterol microembolization.

Hypertensive nephrosclerosis may be responsible for a progressive renal disease in only a subset of hypertensive patients. In these patients, hemodynamic factors might co-cluster with other non-hemodynamic factors, such as genetic determinants, metabolic abnormalities and local immune reaction, thus inducing progressive renal insufficiency.

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DILEMA O ODNOSU BUBREŽNE INSUFICIJENCIJE I HIPERTENZIJE

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Kratak sadržaj: *Podaci izneti u Registru terminalne hronične bubrežne insuficijencije (HBI) pokazuju progresivni i značajan porast u toku više godina incidencije i prevalencije terminalne HBI u vezi sa hipertenzijom, što ide u prilog klasičnog shvatanja da je bubreg žrtva hipertenzije. Dugotrajna hipertenzija može da dovede do terminalne HBI u nekih bolesnika, dovodeći do hipertenzivne nefroskleroze, naročito u amerikanaca afričkog porekla. U velikom broju slučajeva progresivne bubrežne bolesti povezane sa esencijalnom hipertenzijom, naročito u starih osoba bele rase, uzrok terminalne HBI je ateromatozna renovaskularna bolest sa stenozom renalne arterije i/ili mikroembolizacijom iz holesterolskih plakova*

Ključne reči: *Hipertenzivna nefroskleroza, stenoza renalne arterije, holesterolska mikroembolizacija*

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