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Renal Function: The Cinderella of Cardiovascular Risk Profile

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The presence of an altered renal function in essential hypertension, advanced heart failure (HF) and after a myocardial infarction (MI) is associated with higher cardiovascular morbidity and mortality. Indices of altered renal function (e.g., microalbuminuria, increased serum creatinine concentrations, decrease in estimated creatinine clearance or overt proteinuria) are independent predictors of cardiovascular morbidity and mortality in any of the three clinical situations. These parameters should then be routinely evaluated in clinical practice. These facts have several therapeutic implications. First, although there is no evidence-based information on the level of blood pressure that confers optimal renal protection, levels substantially lower than past recommendations are advisable. Second, hypertensive kidney damage should be prevented by early treatment of hypertensive patients, particularly those with microalbuminuria. Finally, to avoid further aggravation of high cardiovascular risk, antihypertensive agents devoid of unwanted metabolic side effects should be used for the treatment of hypertensive vascular damage. In HF, the combination of an angiotensin-converting enzyme (ACE) inhibitor and a beta-blocker seem to be the most renoprotective. Renal outcome is also improved by ACE inhibition after an MI. Finally, renal and cardiovascular outcome seem to run in parallel in all these situations. (J Am Coll Cardiol 2001;38:1782–7) © 2001 by the American College of Cardiology

Cardiovascular mortality is profoundly affected by the presence of advanced renal failure. In patients undergoing maintenance hemodialysis, cardiovascular mortality is approximately 3 to 20 times that of age-matched nonuremic control subjects (1). The increased mortality is associated with a higher frequency of conditions such as myocardial infarction (MI), left ventricular (LV) hypertrophy, and congestive heart failure (CHF). Hypervolemia, arterial hypertension, and dyslipidemia are among the most relevant causes leading to increased cardiovascular morbidity and mortality in advanced renal failure. Recent analyses have shown that renal function is a major determinant of cardiovascular outcome in patients with essential hypertension (2–4) or with heart failure (HF) (5,6) in the absence of primary renal disease. A minor increase in serum creatinine above normal values and, conversely, a slight decrease in creatinine clearance were powerful predictors of future cardiovascular death. This brief review summarizes the available evidence in this field, which is highly relevant because renal data are easy to obtain and provide valuable information.

DIAGNOSIS OF RENAL DAMAGE IN CLINICAL PRACTICE

The diagnosis of renal dysfunction in patients with different forms of cardiovascular disease is based on two findings: 1) elevated serum creatinine or a decrease in glomerular filtration rate (GFR), usually measured as creatinine clearance and/or 2) the detection of an elevated urinary excretion of albumin below (microalbuminuria, 30 to 300 mg/day) or above (macroalbuminuria, >300 mg/day), the usual laboratory methods to detect proteinuria. Mild renal insufficiency has recently been defined as serum creatinine (SCr) values >1.5 mg/dl (132 μmol/l) in men and >1.4 mg/dl (123 μmol/l) in women (7,8), or by the finding of estimated creatinine clearance values below 60 to 70 ml/min (2,6). Whereas an elevated SCr concentration points to a reduced GFR, an increased rate of albumin or protein excretion points to a derangement in the glomerular filtration barrier (9). Microalbuminuria has been shown to correlate with the presence of nephrosclerosis (10), while the presence of proteinuria generally indicates the existence of established renal parenchymatous damage (9). On the other hand, the finding of a SCr value within the normal range can be accompanied by a diminished GFR value, particularly in elderly patients (11). An estimate of creatinine clearance in the absence of 24-h urine collection can be obtained based on prediction equations corrected for age, gender and body size (8). Finally, hyperuricemia (defined as a serum uric acid level in excess of 7 mg/dl) is frequently seen in untreated hypertensives and has also been shown to correlate with the existence of nephrosclerosis (12).

RENAL FUNCTION AS A PREDICTOR OF CARDIOVASCULAR RISK IN ESSENTIAL HYPERTENSION

The kidney and high blood pressure (BP) are closely related. A defective capacity to handle the dietary sodium normally resulting from intrinsic renal abnormalities (13) or an

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
BP = blood pressure
CHF = congestive heart failure
GFR = glomerular filtration rate
HF = heart failure
LV = left ventricle, left ventricular
LVEF = left ventricular ejection fraction
MI = myocardial infarction
SCr = serum creatinine

inadequate response of the kidney to an extrarenal mechanism triggering the hypertensive process (14), are among the most important mechanisms in the initiation and maintenance of essential hypertension. Furthermore, renal vasoconstriction is found at the initial stages of essential hypertension, and this is reversed by the administration of calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors (14). In more advanced stages of the disease, renal vascular resistance is permanently elevated as a consequence of structural lesions of the renal vessels (nephrosclerosis). Such structural damage may underlie the clinical finding of microalbuminuria (10), or the development of overt proteinuria, as well as an increase in SCr or a decrease in creatinine clearance.

Before antihypertensive treatment became available, renal involvement was frequent in patients with primary hypertension. Perera (15) found that proteinuria was present in 42%, and chronic renal failure in 18%, in a series of 500 untreated patients followed until death by the investigator. In this series, life expectancy after the onset of renal involvement was reported to be no more than five to seven years. With the advent of antihypertensive therapy, cardiovascular and renal prognosis of hypertensive patients improved dramatically. There is agreement that renal prognosis is excellent when hypertension is treated. Today, only a small percentage of treated hypertensive patients, about 3%, develop chronic renal failure defined by SCr values (2). However, this percentage has been found to reach 10.7% of patients included in the Heart Outcomes Prevention Evaluation (HOPE) study (4), about 8% of the population included in the Framingham Heart Study (8), and 3% in the general U.S. population according to National Health And Nutrition Examination Survey (NHANES) III data (16). The results of this survey also demonstrate that such a high prevalence is not explained by the simultaneous presence of diabetes but that it is related to inadequate treatment of high BP (16). When GFR is determined by estimated creatinine clearance the percentage of hypertensive patients with a diminished renal function was ≥13% in the Hypertension Optimal Treatment (HOT) study (2), and ≥36% in the HOPE study (4). Interestingly, this parameter is diminished in >50% of the U.S. population above 50 years of age (17). These data help explain the progressive increase in prevalence of nephrosclerosis as a cause of end-stage renal failure in patients entering dialysis programs both in the U.S. and in Europe (18,19).

In the Hypertension Detection and Follow-up Program trial (20), the presence of elevated SCr values (>1.7 mg/dl) at baseline was found to be a very potent predictor for five- and eight-year all-cause mortality. In the Cardiovascular Health Study, baseline SCr values >1.7 mg/dl were associated with a 70% increase in risk for all-cause mortality in elderly men and women followed for five years (21). The risk conferred was similar to that associated with the presence of CHF at baseline. Data from the HOT study (2) have confirmed these findings, demonstrating that SCr values above the cutoff point for mild renal insufficiency predict an elevated cardiovascular risk even when BP control is excellent. In fact, in the HOT study, SCr values were the most powerful predictor of mortality, stronger than any of the known accompanying risk factors (2). The investigators also assessed the prognostic value of a diminished creatinine clearance, as estimated by the Cockcroft and Gault formula (8). Values <60 ml/min were associated with a significantly higher cardiovascular risk (2). In the general population, the presence of an elevated SCr concentration is also associated with a high prevalence of cardiovascular disease (7), as in the case of essential hypertension. This has been attributed to the fact that elevated SCr concentrations coexist with several other cardiovascular risk factors (7,22).

The relevance of proteinuria for cardiovascular prognosis in the community was documented by the Framingham Heart Study (23). The presence of proteinuria in patients with treated essential hypertension varies between 4% and 16% in different series of treated hypertensive patients (24). The International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) study (3) compared the capacity of a long-acting dihydropiridine and a diuretic to diminish cardiovascular events and death in essential hypertension. This study assessed the role of proteinuria as a risk factor. Analysis of the different risk factors revealed that proteinuria conferred a very powerful risk (3).

Attention has recently been drawn to microalbuminuria and its relevance as a predictor of cardiovascular disease (25). Its prevalence varies between 20% and 30% of untreated patients and up to 25% in treated patients. Very recently, it has been shown that the presence of microalbuminuria in primary hypertension carries with it an elevated cardiovascular risk (4,26). According to a persuasive hypothesis, microalbuminuria constitutes the renal expression of a generalized disorder characterized by increased endothelial permeability. This hypothesis provides an explanation for the link between increased urinary albumin excretion and elevated cardiovascular risk (25). Some preliminary data indicate that, in primary hypertension, microalbuminuria is also a predictor of progressive deterioration of renal function in primary hypertension (22,27).

Some data indicate that nephrosclerosis, often found in hypertensive patients, is associated with atherosclerosis of

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the large arteries. Nephrosclerosis is characterized by hyalinization of arterioles and fibroplastic intimal thickening of small arteries. Interestingly, in patients with coronary heart disease, hyalinization of renal arterioles is more marked than in matched control subjects (28). Conversely, in autopsy studies the presence of hyalinization in the renal arterioles is a marker for the presence of advanced coronary atherosclerosis in otherwise asymptomatic young individuals (29).

On the other hand, in individuals with primary renal disease, even very mild degrees of renal failure show an increase in cardiovascular risk, demonstrated by the finding of disturbed lipoprotein (a) concentrations (30) as well as the presence of insulin resistance (31) in proteinuric patients with normal or slightly reduced GFR levels. In early stages of primary renal disease, with GFR values ranging from 60 to 80 ml/min, an increased oxidative stress has also been demonstrated (32), as well as an increment in pulse wave velocity, indicative of diminished arterial compliance (33). The presence of mild renal insufficiency in hypertensives is accompanied by higher initial levels of both systolic and diastolic BP, a predominantly male gender, higher initial levels of serum uric acid and triglycerides, and lower levels of high-density lipoprotein cholesterol (22). A multivariate logistic regression analysis identified systolic and diastolic BP, as well as serum uric acid and triglycerides, as independent predictors for the development of nephrosclerosis. One study (34) showed that insulin resistance in mildly hypertensive subjects is associated with renal injury as a result of impaired renal hemodynamics (i.e., elevation of glomerular filtration fraction and glomerular hyperfiltration). All these findings are accompanied by the absence of a nocturnal decrease in BP, which also contributes to an increasing risk in patients in the initial stages of renal insufficiency (35,36). The data indicate that even minor derangements of renal function are associated with metabolic alterations, show an increase in cardiovascular risk factors, and promote progression of atherosclerosis.

On the other hand, hyperuricemia has been shown to predict a poor cardiovascular outcome in hypertensive patients (37). As previously stated, elevated serum uric acid levels reflect the presence of nephrosclerosis (12), which is frequently accompanied by a diminution in GFR. This fact could jeopardize the predictive capacity of hyperuricemia in favor of that of a diminished renal function (38).

RENAL FUNCTION AS A PREDICTOR OF CARDIOVASCULAR RISK IN HF

Alterations in renal function play a key role in the pathophysiology of HF and are influenced by the treatment of this syndrome. Adequacy of renal function may be a primary determinant of compensation in patients with HF, and therapy capable of improving renal function may delay progression of HF (6,39).

Arterial underfilling is one major factor among the complex mechanisms that lead to renal sodium and water retention in HF (40). Decreased "fullness of the arterial circulation" is sensed by the kidney and erroneously interpreted as due to volume depletion. The kidney paradoxically retains sodium despite the increase of extracellular volume in an attempt to restore arterial filling. In parallel, neurohumoral systems are activated (e.g., the renin-angiotensin-aldosterone system or the sympathetic nervous system), vasopressin is released and endothelin production is enhanced (40). Interestingly, even in patients with only mild ventricular dysfunction, in whom cardiac output is reduced by 20%, renal perfusion was markedly reduced (i.e., by 50%) (41). This finding reflects intense renal vasoconstriction even in the initial stages of CHF (42), which further facilitates the compensatory sodium and water retention to restore arterial filling and maintain BP within a normal range.

The renal capacity to maintain sodium balance in response to a high sodium intake is altered early on in HF (43), and the renal functional reserve is reduced even when the ejection fraction is still normal (43). In more advanced stages of HF, both renal plasma flow and GFR decrease (44). Progressive renal dysfunction is a frequent complication in HF. It is the net result of progressively decreased cardiac output and renal perfusion pressure, as well as renal vasoconstriction facilitated by neurohumoral activation. Recent data have shown that these changes in GFR correlate better with neurohumoral activation than with the left ventricular ejection fraction (LVEF) (5). Advanced age, frequently present in patients with HF, predisposes to the decrease in renal function, as does a history of hypertension or MI (45).

In HF, decreased renal function (i.e., a low creatinine clearance) is associated with increased mortality (5,6). In fact, impaired renal function is a stronger predictor than impaired cardiac function (LVEF and New York Heart Association functional class) (5).

RENAL FUNCTION AS A PREDICTOR OF CARDIOVASCULAR RISK IN VASCULAR DISEASE AND AFTER MI

Baseline renal function measured as SCr or estimated creatinine clearance has shown to be an independent predictor of survival in patients with acute MI (46,47). Estimated creatinine clearance is a powerful predictor of both short- and long-term events in patients admitted to coronary care units. Graded increases in the relative risk for atrial and ventricular arrhythmias, heart block, asystole, development of pulmonary congestion, and cardiogenic shock were observed by McCullough et al. (48) in parallel with graded decreases in renal function. The investigators concluded that patients with estimated creatinine clearance values $<$46.2 ml/min had a higher risk for in-hospital and post-discharge mortality.

The presence of a diminished renal function does not preclude success rates in candidates for percutaneous coro-

nary revascularization but is accompanied by an increased rate of major events during both hospitalization long-term follow-up (49). Chronic renal failure is associated with a particularly high risk of further deterioration of renal function within 48 h of interventional coronary procedures. Such a decline is accompanied by a significantly poorer outcome, especially if dialysis is required (50). In diabetic patients, particularly when they have proteinuria, a similarly poor outcome has been described after isolated artery bypass grafting (51).

The albumin excretion rate has been shown to increase during MI, and this increase yields prognostic information additional to that provided by clinical or echocardiographic evaluation of LV performance (52). In fact, the albumin excretion rate was a better predictor of in-hospital mortality than the Killip class or the echocardiographic LVEF.

RENAL PROTECTION AND CARDIOVASCULAR DISEASE

Strict BP control is necessary to avoid renal damage in primary hypertension. Two issues arise if one tries to achieve maximum improvement in the renal prognosis of hypertensive patients. The first is the BP goal, which affords the best renal protection. According to one study (53), strict BP control, obtained with different antihypertensive agents, did not seem to further protect renal function. By contrast, strict BP control slows the decay in renal function in patients with primary renal disease and heavy proteinuria (54). This has led to the recommendation that in patients with renal failure and proteinuria in excess of 1 g/day, the BP goal should be 125/75 mm Hg (54). The results of the HOT study (2), where patients were randomly allocated to one of three different diastolic BP control goals ($<$90, $<$85, $<$80 mm Hg), have confirmed the relevance of strict BP control on cardiovascular protection and on indices of renal damage (i.e., serum creatinine concentration).

Another issue is whether all antihypertensive drugs are equally effective on renal outcome. Uniformly better outcomes of renal function were obtained when ACE inhibitors were compared to placebo in both diabetic (55) and nondiabetic renal disease (56). In essential hypertension, converting enzyme inhibitors reduced urinary albumin excretion more effectively as compared to diuretics, beta-blockers, and calcium antagonists (57). Furthermore, in hypertensive patients, ACE inhibitors facilitate the regression of remodeling of (58), and improve endothelial function in, resistance arterioles (59). A beneficial effect of this class of drugs in renal outcome in nephrosclerosis when compared to other therapies has also been suggested (60). The presence of mild renal insufficiency (SCr $>$1.4 mg/dl) was accompanied, in the HOPE study (4), by an enhanced protective effect of ramipril to prevent cardiovascular death, total death, and HF requiring hospitalization. Further studies on renal and cardiovascular outcome are needed to elucidate whether renal protection goes hand-in-hand with cardiovascular protection and vice versa.

In HF, renal protection could constitute an important aim of therapy. In the early stages of HF, the blockade of angiotensin II, either with an ACE inhibitor or an angiotensin receptor blocker, was shown to correct abnormal renal handling of sodium (43) and to restore the renal functional reserve (44). This beneficial effect is probably better explained by inactivation of the intrarenal renin-angiotensin system than by a positive effect on the circulating system (61). In more advanced stages of HF, blockade of angiotensin II was shown to improve the prognosis of those patients in whom an improvement in LV function is accompanied by a simultaneous improvement in renal function (61). It is true, however, that a decrease in renal function is seen in about 10% to 25% of patients, usually with advanced HF in whom maintenance of the GFR is dependent upon angiotensin II (62,63). Advanced age, the presence of atrial fibrillation and a low baseline GFR all increase the risk of deterioration of renal function, which is associated with a higher mortality after hospital discharge (64,65). An improvement in renal function has been observed when ACE inhibition was combined with beta-blockade (65). Recent data obtained in patients with HF treated with the vasopeptidase inhibitor omapatrilat (66) look promising and may indicate that combined inhibition of ACE and of neutral endopeptidase could be the best therapy to protect the kidney in HF. Finally, the drop in renal function that is frequently seen after an MI has been shown to be counteracted by the administration of an ACE inhibitor (45).

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