Atherosclerotic Renal Artery Stenosis: Epidemiology, Cardiovascular Outcomes, and Clinical Prediction Rules

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Abstract. Atherosclerotic renal artery stenosis is the most common primary disease of the renal arteries, and it is associated with two major clinical syndromes, ischemic renal disease and hypertension. The prevalence of this disease in the population is undefined because there is no simple and reliable test that can be applied on a large scale. Renal artery involvement in patients with coronary heart disease and/or heart failure is frequent, and it may influence cardiovascular outcomes and survival in these patients. Suspecting renal arterial stenosis in patients with recurrent episodes of pulmonary edema is justified by observations showing that about one third of elderly patients with heart failure display atherosclerotic renal disease. Whether interventions aimed at restoring arterial patency may reduce the high mortality in patients with heart failure is still unclear because, to date, no prospective study has been carried out in these patients. Increased awareness of the need for cost containment has renewed the interest in clinical cues for suspecting renovascular hypertension. In this regard, the DRASTIC study constitutes an important attempt at validating clinical prediction rules. In this study, a clinical rule was derived that predicted renal artery stenosis as efficiently as renal scintigraphy (sensitivity: clinical rule, 65% *versus* scintigraphy, 72%; specificity: 87% *versus* 92%). When tested in a systematic and quantitative manner, clinical findings can perform as accurately as more complex tests in the detection of renal artery stenosis.

Atherosclerotic renal artery stenosis is the most common primary disease of the renal arteries, and it is associated with two major clinical syndromes, ischemic renal disease and hypertension. Renal artery stenosis, ischemic disease, and hypertension may be variously combined (1). Indeed, hypertension does not represent a universal sequela of renal artery stenosis, and renal function may be maintained in the presence of bilateral renal arterial disease. Accurate staging of hypertension and renal dysfunction is fundamental in these patients because the concomitant presence of arterial hypertension and renal ischemia constitutes a situation of high cardiovascular risk. In this review, we will focus on some critical points of the problem from epidemiology to the relationship among atherosclerotic renal artery disease, heart failure, and survival. We will conclude by touching on the importance of clinical prediction rules in the screening of this multifaceted disease.

Arterial Stenosis: How Much Is Enough?

Renal angiography is the undisputed golden standard in the diagnostic work-up for renovascular disease; in clinical practice, it is applied to establish the location and the degree of renal artery stenosis. However, the objectivity of this technique must not be considered beyond question. There is much disagreement among one or two observers as to the severity of stenosis. It has been emphasized that even when using broad categories, *e.g.*, stenosis <70% *versus* stenosis >70%, in a substantial proportion of cases, the evaluation of radiologists differ as to whether a stenosis is clinically important or not (2). Interobserver variability problems apart, establishing the prevalence and the incidence rate of hypertension attributable to atherosclerotic renal disease is also difficult because the degree of renal artery stenosis considered sufficient to cause hypertension is variable across studies. Undoubtedly, the more severe the process, the more likely a given arterial narrowing is to be significant. This is the reason why 75% narrowing is often the selected cut-off. Yet, studies considering a 50% stenosis significant are not rare (3). From a hemodynamic point of view, a given stenosis is significant when there is a demonstrable pressure gradient because the pressure drop beyond the stenosis sets in motion intrarenal adaptive mechanisms eventually leading to renal ischemia and hypertension. In the 1960s, it was observed that at least a 50% narrowing is required in dogs to generate a pressure gradient (4). This finding is in keeping with a recent study in humans (5), which approached the problem by combining three-dimensional magnetic resonance angiography and direct measurement of pressure in the renal artery across the stenotic tract.

Epidemiology of Atherosclerotic Renal Disease

Another factor that hinders the definition of the problem is that there is no study on the prevalence of renal artery stenosis at population level. Such a study would demand the availability of a simple and reliable screening test, and this is beyond available diagnostic technology. The large majority of studies

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performed so far selected patients having the risk factors of this disease (*e.g.*, hypertension or renal insufficiency). The problem is relevant because hemodynamically significant renal artery stenosis may occur in patients with normal BP and/or normal GFR. Autopsy series are often quoted as an unbiased source of information. However such series are based on patients who died in hospital, *i.e.*, on series where atherosclerosis is likely to be a contributor to the cause of death because atherosclerotic complications often lead to hospitalization. Furthermore autopsies are not universally performed on patients who die in hospital. Due to the variability of hospital populations and to a selection process that is difficult to define, it comes as no surprise that the frequency of renal artery stenosis ranged from 12% to 53% in series examining fewer than 300 patients (6–8) and that it was only 4% in a very large series (over 5000 patients) collected over an 8-yr period (9). In the aggregate, it clearly emerges that hypertension is not an obligatory sequela of arterial stenosis of the kidney and that this disease is strongly age-dependent.

Systemic Atherosclerosis and Renal Artery Atherosclerosis

Atherosclerosis is a systemic disease. Although asymmetries in arterial involvement in atherosclerosis may occur, the disease usually proceeds in parallel in various organ systems. From a clinical perspective, knowing the prevalence of renal artery involvement in patients with evidence of atherosclerosis in other organs is important because this knowledge may be incorporated into diagnostic algorithms (see Clinical Prediction Rules). There are a number of studies examining the renal arterial system as a part of abdominal aortography or peripheral arteriography or as an examination complementary to arterial coronography. The prevalence of renal artery stenosis ranges from 14% to 42% in studies performed on patients with aortic (abdominal) or peripheral vascular disease (10–16). It is somewhat less (11% to 23%) in patients with documented coronary artery disease (17–19). Overall, the larger the study, the lower the prevalence of renal artery stenosis (Figure 1). In the most extensive study so far (18), 11% of patients had greater than 50% unilateral narrowing, 2.4% had bilateral 50% to 75%

narrowing, and 1.6% had very severe bilateral stenosis (>75%). Notably, in this study the severity of renal artery disease was predicted by old age, gender, peripheral vascular disease, congestive heart failure, renal insufficiency, smoking, and by the degree of coronary artery involvement.

Evolution of Renal Artery Atherosclerosis

It is fairly well established that atherosclerotic renal artery stenosis is a progressive disease. Sequential angiographic studies have documented that progression of arterial stenosis occurs at a variable rate in patients followed up for a minimum of 6 mo to a maximum of 180 mo (20–25). However, progression is not universal, and it is well documented that, at least in some cases, risk factor modification may allow partial regression of stenosis (26,27). Furthermore, bias may inflate the estimate of the risk of progression because patients who are felt to be at high risk are more intensively investigated. Noninvasive techniques may give an unbiased estimate of the progression of the disease. In this regard, well-conceived echo-color Doppler studies (28,29) have shown that about one fourth of patients with nonsignificant stenosis develop a degree of narrowing greater than 60% after 1 yr of follow-up and that about one patient out of ten with significant stenosis at baseline develops complete arterial occlusion within 2 yr. A large study in over 1000 patients showed that the severity of stenosis is linked to the severity of renal insufficiency because serum creatinine was about 40% higher in patients with significant stenosis (>75% RAS) than in those with a less severe degree of arterial narrowing (30). Overall these findings indicate that it is unlikely that atherosclerotic renal disease stabilizes without specific therapeutic interventions.

Beyond the Stenosis: Parenchymal Renal Damage and Medium-Small Vessel Disease

The degree of arterial narrowing has long been considered the leading factor, if not the sole, responsible for renal function loss in patients with atherosclerotic renal artery stenosis. However, clinical studies performed during the last 20 yr have demonstrated that renal function after revascularization rarely shows significant improvements. Single-kidney GFR measured by reliable isotopic techniques remains almost unchanged after successful angioplasty (31,32). Accordingly, the severity of proximal renal artery stenosis is poorly related to GFR (creatinine clearance) because GFR is similarly reduced in patients with mild and severe stenosis and in those with severe bilateral stenosis (33). These observations may appear at odds with clinical experience because renal disease progression is very often faster in patients with severe stenosis. The contradiction may be only apparent because the severity of stenosis probably represents an indicator of other processes responsible for the evolution of renal insufficiency, *e.g.*, heart failure and nephrosclerosis in the controlateral kidney. The above-mentioned radioisotopic single-kidney studies (32) provide firm evidence that renal parenchymal damage is the major factor responsible for renal function loss in atherosclerotic renal disease, but these findings should not be interpreted as evidence that interventions aimed at restoring arterial patency are of inherently
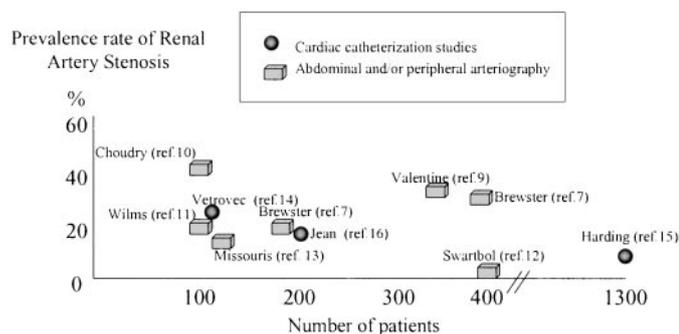

Figure 1. Prevalence of atherosclerotic renal artery stenosis in patients who underwent abdominal aortography or peripheral or coronary angiography. The probability of renal arterial involvement tends to be lower in larger studies.

limited value. The scope of angioplasty or surgery is to slow the rate of loss of renal function rather than improving it. Renal revascularization by restoring parenchymal blood flow reverses only the ischemic component of kidney damage. Apart from stenosis, many factors may conjure to damage the kidney. Thus cholesterol embolization is increasingly recognized as a significant factor in the evolution of renal failure in these patients (31). On the other hand, damage to medium and small arteries in the kidney, *i.e.*, nephrosclerosis, is an important reason why angioplasty does not restore normal renal function in most cases. Nephrosclerosis runs in parallel with systemic atherosclerosis. Indeed in about 300 protocol autopsies in the Honolulu Heart Study (34), it was found that in subjects with hypertension and diabetes hyalinization of arterioles and fibroplasia of small arteries in the renal cortex is associated to BP, glucose level, and alcohol intake. Importantly, these associations appeared to be independent predictors of hyalinization in renal arterioles, giving support to the hypothesis that this type of renal vasculopathy may be a marker for atherosclerosis in other vascular beds.

Renal Atherosclerosis as a Predictor of Cardiovascular Outcomes and Death

Heart Failure and Atherosclerotic Renal Artery Stenosis

Pickering *et al.* (35) were the first to draw attention to pulmonary edema as a complication of bilateral renal artery stenosis. This complication has been attributed to sodium retention and to an increase in permeability in pulmonary microcirculation promoted by angiotensin II. The hypothesis that renal artery stenosis may be instrumental in precipitating heart failure is supported by the fact that renal angioplasty is associated with an objective amelioration of cardiac insufficiency in patients with severe renovascular disease (35–37). Suspecting renal arterial stenosis in patients with recurrent episodes of pulmonary edema is also justified by recent observations showing that the prevalence of atherosclerotic renal disease in elderly patients with decompensated cardiac failure is 34% (38). The identification of these patients is also important because they are at risk of acute renal failure when treated with ACE inhibitors. The overall risk of ACE inhibitor–induced acute renal failure in patients with heart failure is about 2% (39). Notwithstanding the rarity of this complication, serum creatinine should be frequently monitored in patients with compromised left ventricular function on treatment with ACE inhibitors or angiotensin II receptor antagonists.

Survival

As discussed, atherosclerotic renal disease is frequently associated with other cardiovascular complications. For this reason, the presence of renal arterial disease may be considered a risk marker for all-cause and cardiovascular mortality. Five-year survival in two historical prospective studies was 7% lower in patients with renal artery stenosis than in well-matched essential hypertensives (40) and 23% lower than in the general population (41). A prospective study by Conlon (42) in 900 patients submitted to coronary angiography and abdominal aortography has fully confirmed these findings. Indeed 4-yr survival was 21% lower in patients with renal artery stenosis than in patients without renal artery involvement. Furthermore, atherosclerotic renal disease had a strong independent effect on long-term survival independently of coronary artery disease. More recent observations by the same group have shown that the probability of survival is proportional to the severity of arterial narrowing (30). These observations are in line with experimental and clinical data, suggesting that renal ischemia may act as a direct trigger of cardiovascular events in renovascular disease. However interesting they may seem, these observations still leave open the question as to whether or not angioplasty or renal artery surgery may reduce the high mortality in heart failure because to date there is no prospective study on the effect of revascularization procedures on survival in these patients.

Clinical Prediction Rules

In recent years, Echo-color Doppler has emerged as a reliable method to orient the diagnostic work up of patients with suspected renovascular stenosis. However, this method is partially operator-dependent, and it is difficult to apply on a large scale. Using noninvasive tests for the screening of atherosclerotic renal disease in an indiscriminate manner would have a major impact on cost and on the workload of nuclear medicine, radiology, and internal medicine departments. As already mentioned, the probability of diagnosing renal artery stenosis depends on the particular clinical setting in which the disease occurs. The likelihood of atherosclerotic renal disease in a patient with coronary or cerebrovascular disease is higher than that in patients without such atherosclerotic complications. This pretest probability is important because the posttest probability of the disease results from the product of pretest probability and the likelihood ratio of the tests being applied (Figure 2). Prediction rules may greatly help the clinician to select patients for angiography. The most quoted clinical features suggestive of renovascular disease are those reported by the investigators of the time-honored Cooperative Study on Renovascular Hypertension (43). These features were identified by comparing a group of 339 essential hypertensive patients with a group of 175 patients with renovascular hypertension (*i.e.*, hypertension treated by renal artery surgery), and this latter group was characterized by age, hypertension of short duration or accelerated hypertension, retinopathy, presence of coronary, peripheral, and cerebrovascular disease. The validity of this set of clinical findings suggestive of renal artery stenosis in the Cooperative Study has never been formally tested in a prospective study. Furthermore, this information gap still remains to be bridged because until now no such study exists. Increased awareness of the need for cost containment has renewed the interest in the clinical signs of renovascular hypertension. The DRASTIC study is the most recent attempt at validating clinical prediction rules. In this study, the clinical characteristics of 477 patients selected because drug-resistant hypertension or an increase in serum creatinine during therapy with ACE inhibitors were accurately analyzed (44). A regres-
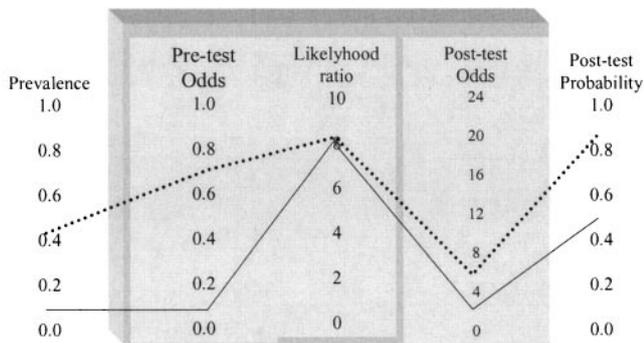
Formulas and definitions
- Pre-test odds: prevalence/1-prevalence
- Likelyhood ratio (LR): sensitivity /(1- specificity)
- Post test Odds: pre-test odds x LR
- Post-test probability: post-test odds/(post test odds +1)

Figure 2. Performance of a diagnostic test in two different clinical settings. The likelihood ratio of the test is 8 (identical in both situations). In the first situation, the prevalence rate of the disease is 10%; in the second situation, the rate is 40%. As shown in the figure, the posttest probability is low (47%) in the first situation and high (84%) in the second. The formulae for the calculation of pretest and posttest odds and likelihood ratio are also presented.

sion model predicting the probability of renal artery stenosis was developed; from this model, a clinical prediction rule was derived. The validity of the model was tested by bootstrapping techniques, *i.e.*, by developing the regression model in a randomly selected sub-sample of patients and then testing the prediction power of the model in patients not included in the fitting procedure. This approach is an important step forward, but it still does not represent the ideal test because clinical findings do not represent an exception to the rule that independent and prospective assessment is the gold standard for validating diagnostic procedures. The important result of this study is that the clinical rule predicted renal artery stenosis as efficiently as renal scintigraphy (sensitivity: clinical rule, 65% *versus* scintigraphy, 72%; specificity: 87% *versus* 92%). When tested in a systematic and quantitative manner, clinical findings can perform as accurately as more complex tests in the detection of renal artery stenosis.

Knowledge on the clinical evolution and on the cardiovascular sequelae of atherosclerotic renal disease has made substantial progress in recent years. The impact of angioplasty or surgery on heart failure and on survival in high-risk patients remains to be investigated in appropriate clinical trials. In an era of expanding diagnostic technology, renewed scientific interest in clinical findings may produce a refreshing reanalysis of the diagnostic and prognostic pathways of this complex disease.

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