EDITORIAL COMMENT

Renal Artery Stenosis: “Fortuitous Diagnosis,” Problematic Therapy*

Larry A. Weinrauch, MD, FACC, John A. D’Elia, MD
Cambridge and Boston, Massachusetts

The carefully designed study by Buller et al. (1) in this issue of the Journal suggests that 60 additional renal artery stenosis (RAS) cases may be found per 1,000 cardiac catheterizations (2,428 patients screened, 1,149 met at least one selection criteria, 298 excluded, resulting in 120 patients being newly diagnosed, more than half with stenoses >70%). How many we could find during noncardiac angiography or during the imaging of patients studied for unrelated problems remains unstudied.

See page 1606

“Fortuitous diagnosis” of RAS has become commonplace, aided by technical advancement (e.g., digital computed tomography, magnetic resonance reconstruction, color flow duplex imaging). Recognition of the association among carotid, coronary, and peripheral disease with RAS inevitably leads to more attempts at renal vascular intervention, particularly in patients over 70 years of age.

EXPLORING THE BENEFITS OF REVASCULARIZATION

The goals for renal revascularization should be predefined. Soft end points, such as short-term arterial patency, stability of renal function, or doses of antihypertensives, have been the primary goal. Short-term arterial patency is an insufficiently beneficial result to be a hard end point. Long term, patency needs to be assured. We cannot depend upon such nonspecific, insensitive tests as serum creatinine to determine whether stents remain patent, renal function has changed, or hemodynamics altered.

Is reduction in number, dose, or type of antihypertensive medicine required really an achievable result? Requirement for less antihypertensive medication to achieve target blood pressure goals would appear to confer benefit, especially if worrisome side effects could be averted. A recent review quoting eight studies of patients with RAS provides little support for greater effectiveness in blood pressure control or preservation of renal function when angioplasty is compared with drug therapy, particularly in individuals presumed to have small-vessel atherosclerosis, such as those with metabolic syndrome or previous cardiovascular complications (2). In one of the studies reviewed, there was no difference in renal function or level of blood pressure control for 106 RAS patients randomized to drug therapy versus angioplasty and followed for one year. Although the number of antihypertensive drugs was lower in the instrumented group, this did not achieve statistical significance (3). In one meta-analysis (4), 210 patients studied in randomized controlled trials demonstrated insignificant differences in blood pressure and renal function. In these trials, a decrease in antihypertensive agent use observed with angioplasty (with or without stent) also was statistically insignificant. Experience has demonstrated that less than half of patients undergoing percutaneous transluminal renal angioplasty benefit with respect to hypertension control or rescue of an ischemic organ (5,6).

Is a reduction in number, dose, or type of antihypertensive medicine really a beneficial result? Revascularization has been reported to reduce but not eliminate medication use. The reduction of medicines used for hypertensive control may be deleterious in populations with the highest reported mortality. Renin angiotensin system activation and beta-adrenergic blockade withdrawal by cessation of antihypertensive medications adversely affect survival in patients with associated vascular or renal disease. Thus, unless revascularization improves the tolerance of beneficial medications, we question whether their elimination represents an acceptable hard end point.

Review of the literature found a high incidence of cardiovascular death with no evidence for prolongation of life after renal revascularization. Renal artery stenosis patients in Sweden have a risk ratio of 5.7 for cardiovascular mortality when compared with an age-matched normal population (7). Two-year survival with medical therapy was 82% to 96% depending upon the presence of bilateral, unilateral, or no significant arterial obstructive disease and renal dysfunction in one study from Japan (8). A similar study in the U.K. lists a 31% five-year survival (9). In Germany, five-year survival after percutaneous transluminal renal angioplasty with stent was 89% to 96% for patients with a serum creatinine <2.5 mg/dl but as low as 30% if the creatinine was above 2.5 mg/dl (10). In the U.S., even with the successful use of stents, patients with serum creatinine of >2 mg/dl had a four-year survival of only 25% (11). Patients with RAS that is associated with peripheral, carotid, or coronary atherosclerosis or severe parenchymal disease have a poor prognosis with or without renal revascularization. We need matched studies of long-term survival before we recommend RAS intervention in addition to medical therapy. Existing studies suffer from small size, insufficient duration (12), or no control group (13).
DEFINING RISKS

Percutaneous transluminal renal angioplasty has supplanted bypass as a result of its benefits in terms of length of stay, patient comfort, and decrease in morbidity. Morbidity is not insignificant. Percutaneous transluminal renal angioplasty is associated with fairly high rates of major (5% to 8%) or minor problems (10% to 15%), ranging from contrast toxicity, hemoptoma, dissection, and renal embolism/infarct leading to reduced kidney function or frank renal failure, which may require surgical intervention, to recurrent stenosis, stent migration, or death (1% to 2%) (5,14,15). Studies from the U.S. and Australia demonstrated restenosis rates of 21% to 29% (16,17).

FUTURE DIRECTIONS

The patients identified by Buller et al. (1) represent a special high-risk group defined by their need for coronary angiography. In such patients, and in those defined by carotid and peripheral vascular disease, cardiac, not renal, issues will decide mortality. Whether renal artery interventions would aid such patients in terms of quality or length of life remains to be documented. The study by Buller et al. (1) designed to identify the prevalence of RAS in a carefully predefined population should not be generalized to populations with greater prevalence of renal disease, such as patients >80 years of age with glomerulosclerosis and relatively silent RAS does not address the consequences of RAS in a population.

How should we interpret this data? Perhaps the best framework is on the basis of the last 30 years of outcome research in coronary arterial disease. Numerous studies have demonstrated that the number of vessels involved, morphology of the obstruction, size of the distal vessel, and function of the left ventricle strongly influence survival. Initial enthusiasm for coronary artery surgery and eventually interventional techniques has been tempered by the results of large studies demonstrating groups of patients who are not likely to derive benefit from aggressive revascularization. Temporary changes in myocardial function, such as stunning and hibernation, have been recognized.

Similar concepts should be as apparent in native or transplanted kidneys. Although much literature exists for renal biopsy and metabolism, there is no renal test similar to Doppler echocardiography to reliably assess functional improvement. Perhaps as a result of this lack, studies suggesting correction of RAS to preserve renal function have been unconvincing. The failure of renal arterial bypass to cure renovascular hypertension and glomerular/tubulointerstitial fibrosis may be dependent upon previous parenchymal damage, as is the case in the myocardium. No benefit from renal revascularization occurs once the kidney loses glomerular function, be it from infarct or irreversible medical renal disease. A shrunken kidney, a cortically necrosed kidney, or a kidney proven by biopsy to have irreversible damage will benefit from revascularization as little as nonviable myocardium. The renin-angiotensin system of a diseased kidney (glomerular or tubular) will have the same lack of benefit as revascularization of coronaries in cardiomyopathy. Investigators in this field are in need of a technology breakthrough, such as use of antioxidants (vitamins C and E), that may preserve kidney function by inhibiting the inflammatory process, which results in tubulointerstitial fibrosis in the setting of RAS (18), providing the patient has been identified early enough in the course of ischemic injury.

In the group studied, the vast majority of renal angiograms would be unnecessary if clinicians used the criteria listed: severe hypertension, unexplained renal dysfunction, acute pulmonary hypertension with pulmonary edema, or severe coronary atherosclerosis in patients scheduled to undergo elective coronary arterial studies (1). The study was not designed to determine whether patients with any of these criteria would benefit from renal revascularization.

Resistance index by Doppler ultrasound should be required before and after embarking upon intervention (19). Either the ultrasound for renal cortical thickness or the nuclear scan for relative perfusion may identify kidneys irreversibly scarred by prior ischemic disease. We believe indiscriminate testing for RAS or fortuitous documentation of lesions leads to procedures laden with morbidity, high cost, and mortality. The only benefit that should be accepted as a reason for revascularization in a patient with RAS is one that can be measured. These would include salvage of a single kidney (native or transplant) to avoid dialysis, clinical consequence of inadequate blood pressure control (pulmonary edema, encephalopathy, acute renal failure, myocardial infarction) with multiple drug combinations, or for prolongation of event-free life (should such eventually be demonstrated). In the absence of randomized controlled studies, clinicians would do well to follow the advice of Buller (1) by pursuing “long-term follow-up of this cohort to determine the significance of RAS with respect to specific heart and kidney disease outcomes” in the management of elderly high-risk patients.

Reprint requests and correspondence: Dr. Larry A. Weinrauch, 521 Mount Auburn Street, Watertown, Massachusetts 02472. E-mail: lweinrauch@hms.harvard.edu.

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