JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 1, NO. 3, 2008

ISSN 1936-8798/08/$34.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2008.04.004

EDITORIAL COMMENT

Atherosclerotic Renal Artery Stenosis

Where's Waldo?*

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We have all treated patients who dramatically improve declining renal function, previously uncontrollable hypertension, or episodic flash pulmonary edema after stenting a severe atherosclerotic renal artery lesion(s). Experience with these success stories has proven that atherosclerotic renal artery stenosis (RAS) in some patients (the Waldos in the crowd of patients with atherosclerotic RAS) can impair renal perfusion and activate the renin-angiotensin system to amplify hypertension. However successful stenting of atherosclerotic renal artery lesions rarely cures hypertension and improves blood pressure in only 50% to 70% of patients (1), whereas renal function is improved in only 25% of those with impaired glomerular filtration at baseline (2). In fact, renal function deteriorates in 10% to 20% of patients after "successful" stenting. Many different issues contribute to clinical outcome after renal artery stenting, and more reliable predictors for selecting patients who are likely to clinically benefit from stenting atherosclerotic RAS are needed. We should require more than simply visualizing a stenosis before stenting is performed (3).

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Renal artery angiography is often performed in a single-plane projection without orthogonal views. The stenosis usually begins at the aorto-ostial junction and is eccentric, both factors making quantification imprecise. It is likely that some patients undergoing renal artery stenting do not in fact have a severely flow-limiting stenosis. Mitchell et al. (4) measured renal artery fractional flow reserve (FFR) after papaverine-induced hyperemia in 17 patients with uncontrolled hypertension and atherosclerotic lesions. Patients with an FFR <0.8 had subsequent blood pressure improvement in 86% of patients after stenting, compared with 30% with improvement in those with FFR >0.8. In that study, quantitative angiography was not able to predict responders from nonresponders even though FFR was able to. Thus, precise functional assessment might help in the selection of patients more likely to improve after renal artery stenting in the future. More scientific information is needed to clarify the role of FFR measurement in patient selection for atherosclerotic renal artery stenting (5).

Even significant RAS does not always cause hypertension in an individual patient. Essential hypertension might be the predominant factor in some (many?) of these patients. Renal dysfunction is especially common in elderly hypertensive patients, and renal failure alone without RAS can cause hypertension. Because renal function remains unchanged in most patients after successful stenting, this contributor to hypertension remains unchanged in the majority of patients presenting with renal dysfunction and atherosclerotic RAS. It is likely that a significant number of patients with co-existent RAS and hypertension do not have flow limitation as their major stimulus for elevated blood pressure.

Although theoretically appealing, documentation of activation of the renin-angiotensin system has not been consistently predictive of a favorable response to renal artery stenting. Even in 2-kidney-1-clip experimental hypertension, activation of multiple compensatory mechanisms can normalize renin in the chronic phase of established hypertension. Elevated Doppler-derived renal resistive index was initially touted as a predictor of a poor response to renal stenting, but subsequent data suggest this is not the case. Elevated brain natriuretic peptide (BNP) in the absence of heart failure might be a clue that RAS is significant in some patients (3), but diastolic dysfunction is so common in hypertensive atherosclerotic RAS patients that the predictive accuracy of an elevated BNP for improvement after stenting is likely to be low. Thus, we do not have, with the possible exception of FFR, a sensitive or specific test to predict the response of an individual patient to renal artery stenting.

In contrast to the improvement in percent stenosis that we reliably see after renal artery stenting, we might also embolize atherosclerotic debris distally into the renal parenchyma, impairing renal function in some patients. Embolization can be identified by angiography in a minority of patients, but angiographically silent emboli could worsen renal function and/or exacerbate hypertension. Even today there is no consensus that emboli protection devices are useful in renal artery stenting. The CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial initially required renal artery protection during stenting, but this requirement has been changed to an option at the discretion of the individual operator. Renal protection devices have not been systematically evaluated, and no specific protection device has been developed for the renal circulation. Despite the fact that emboli protection devices

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 1, NO. 3, 2008
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have been used for more than 8 years in other vascular beds, no prospective randomized trial has been conducted in renal arteries, and the possible efficacy of renal emboli protection remains unknown.

Because of the enthusiasm of interventional cardiologists for stenting renal artery atherosclerotic lesions, we have come under attack from nephrologists and the rest of the conservative medical community. This criticism is not without substance. The Dutch multi center DRASTIC trial failed to show an improvement with renal artery angioplasty over medical therapy (6). The preliminary results of the ASTRAL trial recently presented at the American College of Cardiology meeting in 2008 also suggested no improvement in blood pressure control or renal function with renal artery stenting versus medical therapy in patients with RAS and no "clear indication" for stenting. "Clear indications" included pulmonary edema and acute renal failure in association with severe RAS (7). The onus has now clearly shifted to the interventional community to scientifically define which patients might benefit from atherosclerotic renal artery stenting and whether emboli protection devices are of value in preserving renal function.

In this issue of *JACC: Cardiovascular Interventions*, Mahmud et al. (8) present results on renal frame count and renal blush grade as quantitative measures to predict the success of renal stenting to improve hypertension. The authors used standard angiographic methods validated in the coronary world to assess renal flow by quantitative angiography. Digital angiograms acquired at 30 frames/s and analyzed offline by the method first described by Mulumudi and White (9) in hypertensive renal fibromuscular disease patients were used. Hypertensive patients with unilateral RAS had an elevated baseline renal frame count of 26.6 ± 9.1 (normal = 20.1 ± 5.4) frames/s, and renal frame count was reduced to 21.4 ± 6.7 after stenting ($p < 0.001$). Clinical responders identified as those with a systolic blood pressure reduction >15 mm had a decrease in renal frame count of 7.7 ± 4.6 compared with 1.7 ± 5.1 frames/s in nonresponders($p = 0.009$). More than 78% of patients with >4 frames/s renal frame count decrease after successful stenting were responders. The study is limited in patient numbers, but the results suggest that reduced renal artery perfusion reflected by increased renal frame count might predict those patients most likely to respond to renal artery stenting with an improvement in blood pressure. A reduction in renal frame count >4 frames/s also predicted a good clinical response. These hypothesis-generating data require further validation, but it involves a method (digital angiography) that we all have available but have not used extensively. Not all laboratories performing renal stenting use 30-frames/s digital acquisition, but this could be standardized easily and studied prospectively.

In addition, Mahmud et al. (8) measured renal blush grade before and after stenting. They noted a low renal blush grade at baseline (1.63 ± 0.71; normal = 2.33 ± 0.66) that was improved after renal stenting to 2.13 ± 0.85 ($p = 0.03$). Although renal blush grade was not predictive of clinical response in this small study, one might hypothesize that reduction in renal blush grade after stenting might provide a quantitative index of the extent of distal embolization. Such a surrogate end point might be helpful in clarifying the potential benefit of emboli protection devices in renal artery stenting in the future.

The authors are to be congratulated on this scientific endeavor to identify quantitative measures that might help us in defining the role of renal artery stenting for atherosclerotic lesions in the future. A renewed effort of interventionalists to study the effects of renal artery stenting carefully and scientifically needs to be mounted in order to clarify the possible role of stenting in atherosclerotic renal artery disease.

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REFERENCES

1. Rocha-Singh K, Jaff MR, Rosenfeld K, and the ASPIRE-2 Trial Investigators. Evaluation of the safety and effectiveness of renal artery stenting after unsuccessful balloon angioplasty: the ASPIRE-2 study. J Am Coll Cardiol 2005;46:776–83.
2. Isles CG, Robertson S, Hill D. Management of renovascular disease: a review of renal artery stenting in ten studies. Q J Med 1999;92:159–67.
3. White CJ. Catheter-based therapy for atherosclerotic renal artery stenosis. Circulation 2006;113:1454–73.
4. Mitchell J, Subramanian R, Stewart R, White C. Pressure-derived renal fraction flow reserve with clinical outcomes following intervention (abstr). Catheter Cardiovasc Interv 2005;65:135.
5. Subramanian R, White CJ, Rosenfield K, et al. Renal fractional flow reserve: a hemodynamic evaluation of moderate renal artery stenoses. Catheter Cardiovasc Interv 2005;64:480–6.
6. Van Jaarsveld B, Krijnen P, Pieterman H, et al. The effect of balloon angioplasty on hypertension in atherosclerotic renal artery stenosis. N Engl J Med 2000;342:1007–14.
7. Kalra PA. ASTRAL: Stenting makes no difference in renal artery disease. Presented at Late-Breaking Clinical Trials Session: Society for Cardiovascular Angiography and Interventions-American College of Cardiology Innovations in Intervention (SCAI-ACCi2), Chicago, IL. April 1, 2008.
8. Mahmud E, Smith TWR, Palakodeti V, et al. Renal frame count and renal blush grade: quantitative measures that predict the success of renal stenting in hypertensive patients with renal artery stenosis. J Am Coll Cardiol Intv 2008;1:286–92.
9. Mulumudi M, White C. Renal frame count: a quantitative angiographic assessment of renal perfusion. Catheter Cardiovasc Interv 2005;65:183–6.