The Importance of Appropriate Renal Artery Stenting

Considerations for diagnosis and treatment of patients with renal artery stenosis.

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Renal artery stenosis (RAS) is a relatively common disease with a mortality rate of approximately 16% annually, which is mostly related to cardiovascular disease.[1] RAS is associated with both hypertension and chronic kidney disease, the treatment of which has been based primarily on stenting guided by angiography.[2] The guidelines for renal artery revascularization[3] suggest that a hemodynamically significant RAS is defined as the presence of ≥ 50% to 70% diameter stenosis by visual estimation on angiography, a systolic pressure gradient ≥ 20 mm Hg, or a mean gradient ≥ 10 mm Hg measured with a ≤ 5-F catheter or a pressure guidewire. However, one study[4] proposed the notion that the systolic pressure gradient was significantly overestimated when a 4-F catheter is used compared with a 0.014-inch pressure guidewire.

Despite the high procedural success rate of renal artery stenting, an improvement in hypertension has been inconsistent. This most likely reflects the absence of predictors for blood pressure improvement after renal artery stenting. One study[5] reported that stenting of RAS based on visual estimation resulted in blood pressure improvement in 47% of patients at 24 months. However, others have reported an improvement in blood pressure in 62%[6] and 76% of patients at 12 months.[7] These studies required more stringent criteria before stenting, including duplex ultrasound or evidence of a critical RAS based on quantitative renal angiography.

In contrast, the ASTRAL trial[8] randomized 806 patients with RAS to medical therapy versus stenting based on angiographic stenosis and demonstrated no significant benefit from stenting in patients who underwent stenting compared with medical therapy. Because the correlation between renal pressure measurements and angiographic diameter stenosis is poor, it is likely that patients without significant pressure gradient have been included in the ASTRAL trial. Such an inconsistent blood pressure response to renal stenting underscores the value of renal pressure measurements for appropriate patient selection. In particular, in light of the observed 19.7% major adverse events that have been reported after renal artery stenting,[9] renal artery stenting based on renal pressure gradient allows for better patient selection and determines who might benefit most from this procedure.

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ASSESSMENT OF RENAL ARTERY STENOSIS

Both intravascular ultrasound (IVUS) and fractional flow reserve (FFR) are well-validated techniques for assessing the significance of coronary artery stenosis.[10,11] The discordance between high procedure success rates and moderate clinical response rates in patients with RAS may stem from the limitations of angiography for assessing the significance of RAS.

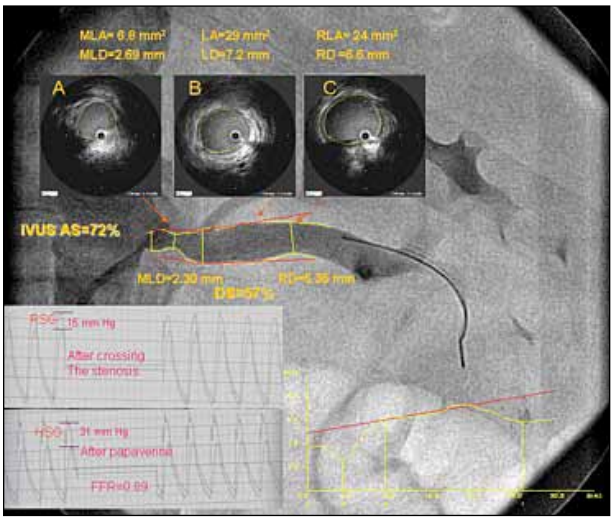

Figure 1. A representative example of quantitative renal angiography, IVUS analysis, and translesional pressure gradient is shown in one study patient with RAS. The minimum lumen diameter and minimum lumen area from the stenotic segment (A) as well as the reference diameter and reference lumen area from the reference segment (B) were selected for both quantitative angiographic and IVUS analyses. Panel C shows the segment with poststenotic dilation. Quantitative renal angiography demonstrates that the diameter stenosis of the renal artery is 57%, not significant by CORAL Study Criteria. IVUS area stenosis and HSG are 72% and 31 mm Hg, respectively; both are indicative of significant RAS. Reprinted from *Journal of the American College of Cardiology,* 53/25, Massoud A, et al. Prediction of hypertension improvement after stenting of renal artery stenosis: comparative accuracy of translesional pressure gradients, intravascular ultrasound, and angiography, 2363–2387, 2009, with permission from Elsevier.[12]

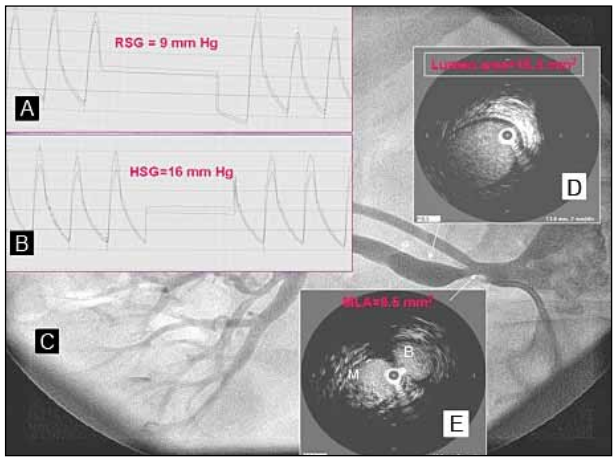

Figure 2. RSG = 9 mm Hg (A); HSG = 16 mm Hg (B). A renal angiogram demonstrates a 70% stenosis of the renal artery at the bifurcation (C). Reference lumen area = 16.3 mm² (D). IVUS at bifurcation demonstrates that minimum lumen area (MLA) at the main branch was 9.5 mm² (E). Reprinted with permission from Tariq S et al. *Catheter Cardiovasc Interv* (2007;69:894–901).[13]

Recently, there has been considerable interest in using endovascular techniques for assessing the significance of RAS. In this respect, a number of studies[13-15] demonstrated poor correlations comparing diameter stenosis by quantitative renal angiography with a number of renal pressure measurements, including resting systolic gradient (RSG), renal FFR, hyperemic mean gradient (HMG), and hyperemic systolic gradient (HSG).

We recently compared the diagnostic accuracy of renal translesional pressure gradient, IVUS, and angiographic parameters in predicting hypertension improvement after stenting of RAS in 62 patients.[12] Following renal angiography, we advanced a 0.014-inch pressure guidewire (PressureWire, St. Jude Medical, Inc., St. Paul, MN) into the renal artery through a guiding catheter. After equalization of pressures, the pressure transducer was advanced through the stenosis, and RSG was measured. Next, a 30-mg bolus dose of papaverine was diluted in sterile water and administered directly into the renal artery to induce hyperemia, as previously reported.[14,15] After papaverine injection, the guiding catheter was retracted from the ostium of the renal artery to prevent dampening of pressures, and then translesional gradients such as HSG, FFR, and HMG were measured.

After obtaining pressure measurements, an IVUS catheter (Atlantis SR Pro, Boston Scientific Corporation, Natick, MA) was advanced into the renal artery over the pressure guidewire. Ultrasound images were recorded after initiation of automated pullback at a speed of 0.5 mm/s, starting approximately 10 mm distal to the lesion. After performing IVUS, all patients underwent renal artery angioplasty followed by stenting using the standard technique. Because the pressure guidewire does not provide enough support for the deployment of peripheral stents, a 0.014-inch Spartacore guidewire (Abbott Vascular, Santa Clara, CA) was advanced into the renal artery, the pressure guidewire was removed, and then stenting of the renal artery was performed using the Spartacore guidewire.

Inclusion of patients for the study was based on the visual estimation of stenosis (RAS with a diameter stenosis of 50% to 90%). Stent size was determined by IVUS based on media-to-media diameter measured at a normal-looking segment distal to poststenotic dilation; stent length was also determined by IVUS (Figure 1). After stenting, the pressure guidewire was readvanced into the renal artery, and HSG was measured to ensure that optimal results were achieved.

As demonstrated in Table 1, an HSG ≥ 21 mm Hg as measured by the pressure guidewire was the strongest predictor of hypertension improvement after stenting of RAS. Although FFR-, HMG-, and IVUS-determined minimum lumen area were predictors of hypertension improvements by univariate analysis, of these parameters, HSG was the only independent predictor of hypertension improvement, suggesting that an HSG ≥ 21 mm Hg is indicative of hemodynamically significant RAS. In contrast, diameter stenosis measured by quantitative renal angiography did not predict hypertension improvement.

At 12-month follow-up, blood pressure, dosage, and the number of antihypertensive medications were significantly lower in patients with an HSG ≥ 21 mm Hg than in those with an HSG < 21 mm Hg. Figure 2 shows a representative case from this study. Although by angiography, the renal artery appeared significantly stenosed, the HSG was 16 mm Hg (nonsignificant). Figure 3 demonstrates another representative case from this study in which angiography showed a 50% RAS but an HSG of 32 mm Hg, which is indicative of significant RAS.

RESTING VERSUS HYPEREMIC PRESSURE GRADIENT MEASUREMENTS

Maximal hyperemia is paramount in determining the physiological significance of a coronary stenosis. A number of studies have demonstrated that after intrarenal papaverine administration, hyperemia can be induced in renal circulation.[16-19] Intracoronary papaverine has been used for the physiological assessment of coronary artery stenosis; however, this was associated with prolongation of the QT interval and induction of polymorphous ventricular tachycardia.[21-25] Adenosine, on the other hand, is now commonly used in lieu of papaverine for the physiological assessment of a coronary artery stenosis. However, intrarenal adenosine can reduce the glomerular filtration rate by constricting afferent arterioles,[26] and thus, it is not a suitable agent to induce hyperemia.

In contrast, studies have shown that intrarenal papaverine significantly increased renal flow reserve.[16-18] Likewise, it has also been demonstrated[19] that intrarenal dopamine significantly increases renal flow reserve in normotensive patients. In line with these observations, we have demonstrated[20] that renin production, an index of renal ischemia, was markedly greater at hyperemia than at rest, suggesting that RAS with an HSG of 21 mm Hg is indicative of hemodynamically significant stenosis (Figure 4). We have also shown[20] strong correlations between HSG and renal FFR, as measured during hyperemia, but found moderate correlations between HSG and RSG, suggesting that hyperemic reserve exists in the renal circulation. Taken together, the results of these studies suggest that hyperemia can be induced by dilating the renal microvasculature and is essential in maintaining renal autoregulation. Therefore, it is conceivable that, analogous to

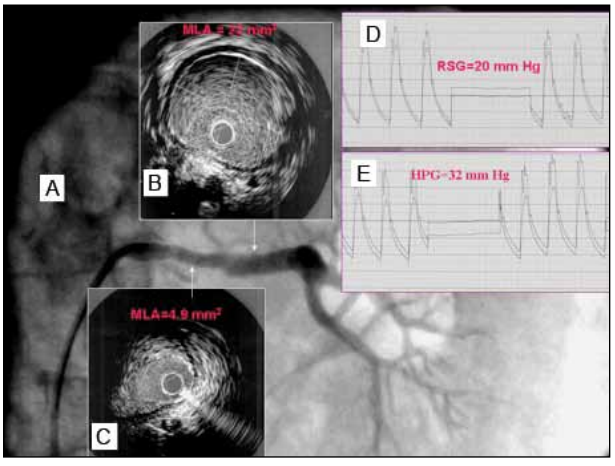

Figure 3. Renal angiography demonstrates a 50% stenosis of the renal artery at the bifurcation (A). Reference lumen area = 22 mm² (B). IVUS at bifurcation demonstrates that MLA was 4.9 mm² (C). RSG = 20 mm Hg (D). HSG = 32 mm Hg (E). Reprinted with permission from Tariq S et al. *Catheter Cardiovasc Interv* (2007;69:894–901).[14]

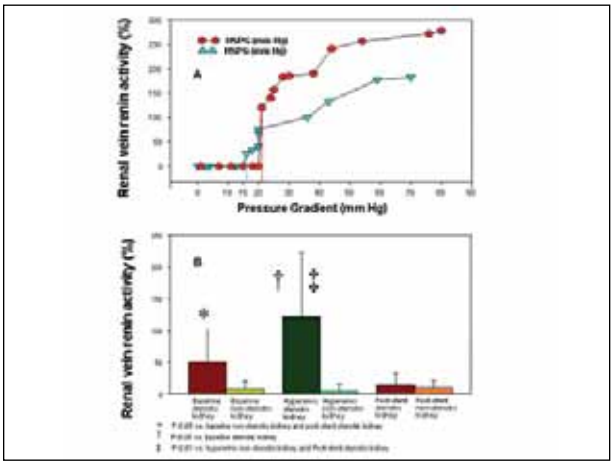

Figure 4. When RSG (shown in triangles) exceeded 16 mm Hg, renal vein renin activity (RVRA) increased modestly (18%) (A). In contrast, when HSG (shown in circles) exceeded 21 mm Hg, RVRA markedly increases (120%). The average RVRA in the stenotic kidneys during hyperemia was significantly greater than that of RSG (B). In addition, the average RVRA in the stenotic kidneys during hyperemia was significantly greater compared with RVRA at resting and after stenting. Reprinted with permission from Kapoor N et al. *Catheter Cardiovasc Interv* (2010;76:726–732).[20]

the coronary circulation, the measurements of hyperemic gradients, such as HSG or renal FFR, can estimate the significance of RAS more accurately than resting gradients.

Papaverine is metabolized in the liver and excreted in the kidney. The elimination half-life of papaverine is 1.5 to 2 hours. The proposed mechanism of papaverine-induced ventricular arrhythmia is linked to the prolongation of repolarization by papaverine.[21,25] Recently, we compared resting and hyperemic pressure gradients induced by intrarenal papaverine for the assessment of RAS in 55 patients.[20] We demonstrated that intrarenal papaverine neither prolonged the QT interval nor induced ventricular arrhythmia. One plausible explanation for the lack of the QT prolongation after intrarenal papaverine resides in the fact that a portion of the papaverine is eliminated by excretion into the urine, but the remaining portion of the drug that returns to systemic circulation via the renal vein is diluted; thereby, the myocardial concentration of papaverine is expected to be considerably lower after intrarenal papaverine.

SUMMARY OF PHYSIOLOGICAL STUDIES FOR ASSESSING THE SEVERITY OF THE RAS

Four recent studies investigated the significance of RAS using the pressure guidewire. Jones et al[27] measured HSG in 22 patients with RAS and demonstrated that after stenting of RAS in 13 patients with HSG > 20 mm Hg, systolic blood pressure significantly improved at follow-up. Mitchell et al[13] reported that stenting in 17 patients with RAS resulted in a significant

TABLE 1. RECEIVER OPERATING CHARACTERISTICS ANALYSES OF THE OPTIMAL CUT POINTS OF PARAMETERS IN PREDICTING HYPERTENSION IMPROVEMENT AFTER STENTING OF RAS

Parameters	AUC	95% Confidence Interval	Cut Point	Sensitivity (%)	Specificity (%)	Predictive Accuracy (%)
Renal Pressure Measurements						
HSG	0.87	0.72–0.96	21 mm Hg	82	84	84
FFR	0.85	0.76–0.94	0.9	73	88	79
HMG	0.81	0.7–0.91	6 mm Hg	80	76	79
RSG	0.81	0.71–0.92	7 mm Hg	78	76	77
IVUS Parameters						
MLA	0.86	0.76–0.95	7.8 mm^2	78	80	79
Area stenosis	0.82	0.71–0.92	67%	75	80	77
MLD	0.78	0.67–0.9	2.7 mm	70	76	72[a]
Plaque plus media area	0.73	0.6–0.85	9 mm^2	73	68	70[a]
Angiographic Parameters						
Diameter stenosis	0.74	0.61–0.86	60%	68	72	69[a]
MLD	0.69	0.55–0.82	2.25 mm	51	80	62[a,b]
Clinical Parameters						
Systolic blood pressure	0.55	0.41–0.7	170 mm Hg	43	68	53[a,b]
Diastolic blood pressure	0.51	0.36–0.66	95 mm Hg	41	64	50[a,b]
Mean blood pressure	0.54	0.39–0.68	118 mm Hg	51	60	54[a,b]

[a]P < .05 vs HSG.
[b]P < .05 vs MLA and FFR.
Abbreviations: AUC, area under the curve; MLD, minimum lumen diameter.

… HSG ≥ 21 mm Hg after administration of intrarenal papaverine was an independent predictor of hypertension improvement.

hypertension improvement in patients who had a renal FFR < 0.8 compared with those with an FFR > 0.8. Although the measurement of FFR is useful in the coronary circulation,[28] we demonstrated that FFR had a lower predictive power for hypertension improvement.[12] This is probably linked to lower vasodilator reserve in the renal circulation than in the coronary microvasculature.[16,19]

Mangiacapra et al[29] investigated the predictive value of translesional gradient on hypertension improvement after intrarenal administration of dopamine (50 µg/kg) or papaverine (30 mg) in patients with RAS and demonstrated that a mean pressure gradient of ≥ 20 mm Hg induced by intrarenal dopamine was highly predictive of hypertension improvement after renal stenting. On the other hand, we demonstrated[12] that hyperemic systolic gradient after intrarenal administration of papaverine had a higher predictive accuracy compared with mean gradient in predicting hypertension improvement.

Furthermore, our data showed that HSG ≥ 21 mm Hg after administration of intrarenal papaverine was an independent predictor of hypertension improvement. The differences between our study and that of Mangiacapra et al lie in the fact that the duration of follow-up in the Mangiacapra et al study was limited to 3 months, whereas in our study, blood pressure improvement was assessed at the end of 12 months. In this respect, a large randomized study is needed to assess the value of translesional pressure gradient measurements during maximal hyperemia induced by either dopamine or papaverine to assess the prediction of blood pressure improvement after stenting of the RAS.

CONCLUSION

Among patients with RAS, regardless of the angiographic severity, a measurement of translesional pressure gradient during hyperemia such as an HSG ≥ 21 mm Hg would indicate a hemodynamically significant RAS. Furthermore, in this setting, HSG can easily be measured after renal angiography with a pressure guidewire, circumventing the need for IVUS or a renal vein renin study to determine the significance of RAS. This would, in turn, facilitate decision making regarding medical therapy versus stenting in patients with RAS. ■

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