Physiologic Assessment of Renal Artery Stenosis

Will History Repeat Itself?*

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Renal artery stenosis resulting in renovascular hypertension is an increasingly recognized clinical problem, with an incidence between 5% and 10% (1). Unilateral renal artery stenosis with 2 normally functioning kidneys can result in renal hypoperfusion and increased release of renin by the affected kidney. The increased renin ultimately leads to elevation of angiotensin II and aldosterone, both of which cause hypertension and kidney dysfunction. Percutaneous revascularization of renal artery stenosis in certain patient populations likely results in improved blood pressure control and preservation of kidney function (2). Accurate diagnosis of clinically significant renal artery stenosis and appropriate selection of patients for revascularization remains challenging in part because angiography continues to serve as the reference standard.

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The insensitivity of angiography to accurately identify which moderate arterial stenoses are hemodynamically significant has been known for many years (3). The value of measuring pressure gradients to characterize the functional impact of a stenosis and the relationship between pressure and arterial flow has also been appreciated for a number of years (4). In coronary arteries, early attempts at using pressure gradients to distinguish flow-limiting stenoses from insignificant ones were hampered by the large size of the catheters being used to measure pressure, which resulted in damped pressures and falsely high gradients (5). In addition, the utility of maximizing flow across a coronary stenosis to simulate stress and measure a peak gradient was not yet widely understood.

With the development of a miniaturized pressure sensor mounted near the tip of a standard 0.014-inch coronary angioplasty guidewire and the introduction of a novel index, fractional flow reserve (FFR), by Pijls et al. (6), in which distal coronary pressure is compared with proximal pressure during maximal hyperemia, measuring coronary pressure to assess the physiologic significance of an intermediate coronary narrowing has now become commonplace. These investigators and others have since shown that pressure-derived FFR correlates well with noninvasive stress imaging studies in a broad range of patients, is more effective than angiography alone for identifying ischemia-producing coronary narrows that require revascularization, and is cost-effective (7–12). In the renal arterial system, the limitations of angiography and the potential usefulness of pressure gradient measurements have also been recognized for many years (13). A subsequent investigation suggested no correlation between renal artery pressure gradients and the severity of renal artery stenosis on the basis of plasma renin levels, systemic blood pressure, renal function, or medication requirements, but the large catheter used to measure distal pressure in this study and other earlier work likely contributed to the obstruction and falsely increased the gradient (14). More recent studies confirm that using a pressure wire to measure the renal artery stenosis gradient is more accurate than the larger catheters previously used, but there remains a paucity of data correlating resting pressure gradients with stenosis severity or outcomes (15,16). Despite this fact, guidelines arbitrarily recommend using a resting systolic pressure gradient of >20 mm Hg to define a significant renal artery stenosis (17). Others have suggested that, in a fashion similar to measuring FFR across an intermediate coronary stenosis, flow across the renal artery stenosis should be maximized and the ratio of distal renal pressure to aortic pressure during hyperemia should be measured (so-called renal FFR) to better characterize the physiologic impact of a renal artery stenosis (18,19). However, because renovascular hypertension and renal dysfunction, the important potential clinical complications from renal artery stenosis, occur due to chronically abnormal renal perfusion in the resting state—unlike myocardial ischemia, which generally occurs during periods of increased myocardial oxygen demand—a resting gradient across a renal artery stenosis or resting ratio of distal/proximal renal pressure should provide sufficient information about the hemodynamic impact of the narrowing.

In this issue of the Journal, De Bruyne et al. (20) apply their extensive coronary experience with the pressure wire in an elegant study, the goal of which is to provide some basis for what defines a clinically significant pressure gradient across a renal artery stenosis. They evaluated 15 patients with unilateral mild to moderate renal artery stenosis, hypertension, and preserved kidney function who were undergoing renal artery stenting. With a novel method, which they first described in coronary arteries, these investigators created increasingly severe renal artery stenoses by inflating a balloon to varying degrees within the stented portion of the renal artery (21). Instead of depicting the severity of the stenosis as the resting gradient, they expressed it as the ratio of the mean distal pressure \(P_d\) measured with a coronary pressure wire to the mean aortic pressure \(P_a\) measured with a guide catheter and in that way...
controlled for differences in the driving pressure. In this manner they created renal artery stenoses with Pd/Pa ratios of 1.0, 0.9, 0.8, 0.7, 0.6, and 0.5 successively for 10 min each. They based their determination of a clinically significant ratio and hence clinically significant renal artery stenosis on the Pd/Pa ratio at which the percent change in renin became significantly elevated.

They found that the percent change in renin from aortic blood increased, but not significantly, with increasing degrees of stenosis. There was, however, a significant and progressive increase in the renin levels measured from the vein of the stenotic kidney starting at a Pd/Pa ratio of 0.80. Interestingly, the renin levels in the vein of the non-stenotic kidney also increased, reaching statistical significance at a Pd/Pa ratio of 0.50. On the basis of these findings, the authors conclude that because the renin levels did not become acutely elevated until after a Pd/Pa <0.90 was achieved, stenoses with ratios of 0.90 or greater are not likely to be responsible for renovascular hypertension and need not be revascularized, even if the percent diameter stenosis appears >50%.

De Bruyne et al. (20) should be commended for their carefully done study and for their forthright and scientific approach to an area that remains controversial. There are a few aspects of the study that deserve further discussion.

First, there was a large variation in the systolic gradient at each Pd/Pa ratio, presumably because of a large variation in systemic blood pressure. For example, with the Pd/Pa ratio of 0.80, the systolic gradient varied from roughly 10 mm Hg to as high as 75 mm Hg, whereas with the Pd/Pa ratio of 0.90 there were a number of patients with a systolic gradient over 20 mm Hg. This finding amplifies the limitation of measuring systolic gradients and might explain in part why previous studies that used pressure gradients to determine treatment strategy showed no benefit with percutaneous revascularization, because some patients with renal artery stenosis and an insignificant decrease in renal perfusion (Pd/Pa ratio >0.90) but a large systolic gradient were incorrectly categorized as having hemodynamically significant disease.

Second, with their unique human model for creating variable renal artery stenoses, the authors were able to document the fraction of perfusion pressure (<90% or Pd/Pa <0.90) below which significant elevations of renin occur acutely, suggesting that stenoses of this degree are likely to cause renovascular hypertension. In this manner, they base their definition of a significant stenosis directly on a pathophysiological response, analogous to ischemic ST-segment changes on an exercise stress test. It will be important to determine whether a Pd/Pa ratio of <0.90 in the setting of renal artery stenosis not only predicts acute elevation of ipsilateral renal vein renin but also predicts improved blood pressure and renal function preservation after revascularization.

Finally, some limitations of the study should be highlighted. The patients included in this study all had mild renal artery stenosis on the basis of the average diameter stenosis, systolic pressure gradient, Pd/Pa ratio, and number of antihypertensive medications (1.9) before stenting, and all had normal renal function. It will be important to test whether the same Pd/Pa cutoff value of <0.90 for determining a hemodynamically significant lesion applies to kidneys that have been exposed to more severe renal artery stenosis and its consequences. We are not provided with the average systemic blood pressure, which would be useful information. For example, in the extreme case that all of the patients had mean aortic pressures of 60 mm Hg, then decreasing the renal perfusion pressure by 20% (Pd/Pa = 0.80) might have a much more dramatic effect on renin release compared with a 20% decrease in patients with a mean aortic pressure of 100 mm Hg.

In summary, De Bruyne et al. (20), in a fashion similar to their coronary research, introduce an invasive, pressure wire–based physiologic index for identifying hemodynamically significant renal artery stenosis. Fractional flow reserve has now been extensively validated, and its clinical utility has been well documented. Hopefully, in the case of this new renal artery stenosis index, history will repeat itself.

**REFERENCES**