Atherosclerotic Renal Artery Stenosis: There is No Obvious Reason to Dilate

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It's narrow – let's dilate it! Very often this seems to be the battle cry of our colleagues, be it the interventional cardiologist, radiologist or vascular surgeon, when facing a narrowed artery. Is this approach justified when the artery in question is an atherosclerotic renal artery?

Atherosclerotic narrowing of one or both renal arteries is a common finding in an older population [1]. It may lead to renovascular hypertension and/or ischemic nephropathy, or both [2], but it may be an incidental finding with no clinical relevance in patients with essential hypertension and/or chronic kidney disease from a variety of other etiologies [3]. It might even be seen in normotensive subjects with no evidence of renal dysfunction [3–5].

Hundreds of papers were published in recent years regarding the diagnosis and treatment of this condition. Many articles report on renal artery stenosis, but use substantially different definitions. The most popular criterion for stenosis is reduction of luminal diameter. However, "significant" stenosis is 50% for some investigators [4,6], but 70% [7] and even 75% for others [8]. Moreover, the diagnosis of "significant" stenosis is made using diverse diagnostic modalities, like Doppler ultrasound, computed tomography angiography, magnetic resonance angiography, digital subtraction angiography and conventional arteriography, which are not interchangeable and difficult to compare [9,10], not to mention inter-observer differences [11]

Any attempt to answer the above question should take into consideration the diverse clinical presentations and outcomes as well as the range of diagnostic criteria and tools. It should be noted that atherosclerosis is not the only cause of RAS; fibromuscular dysplasia accounts for about 10–30% of cases [2,12]. The results of angioplasty in RAS due to FMD (FMD-RAS) are much better than in atherosclerotic RAS [2,13]. Several reports in the literature include both ARAS and FMD-RAS, making the interpretation of the data even more complicated.

As described above, the two main consequences of a narrowed renal artery are hypertension and ischemic nephropathy. For the purpose of this discussion these two clinical syndromes should be considered separately since the goal of treatment is different: to cure, or at least to control, hypertension vs. to save renal function and prevent end-stage renal failure.

The diagnosis of renovascular hypertension should only be made when the stenosis of the renal artery is the only, or at least the main, cause of hypertension, usually via activation of the renin-angiotensin system [2]. As such, renovascular hypertension is quite rare, accounting for 1–5% [5] of all cases of hypertension. However, hypertension on one hand and RAS on the other are common findings in the elderly population. The explanation of this apparent contradiction is that hypertension and ARAS coexist but there is no causal relationship between the two as most subjects actually suffer from essential hypertension, which is very common in the elderly population [2]. With the current armamentarium, it is possible to control hypertension with drug therapy alone in the vast majority of patients, including those with RAS [14]. While many publications addressed the issue of angioplasty vs. drug treatment alone in renovascular hypertension, very few are well-executed prospective randomized controlled trials.

Van Jaarsveld et al. [3] reported the results of a randomized controlled trial of the Dutch Renal Artery Stenosis Intervention Cooperative Study group. The study included 106 patients with hypertension and RAS, randomly assigned to either percutaneous transluminal renal angioplasty or drug therapy. After 1 year of follow-up the conclusions are unequivocal: "In the treatment of patients with hypertension and RAS angioplasty has little advantage over antihypertensive-drug therapy."

The Scottish and Newcastle Renal Artery Stenosis Collaborative study included 135 patients of whom 55 were randomized to intervention or drug therapy alone; the other 80 were managed by the preferred local option but were assessed and followed by the same protocol as the randomized patients [16]. Again, the conclusions are unequivocal: "In hypertensive patients with atheromatous renal artery stenosis, percutaneous renal angioplasty results in a modest improvement in systolic BP compared with medical therapy alone. This benefit was confined to patients with bilateral disease....the use of angioplasty in hypertensive renovascular disease as a reserve procedure for patients whose BP cannot be controlled by medical therapy, or for those whose renal function is deteriorating despite medical therapy, rather than as a primary form of intervention."

Plouin et al. [8] reported the results of the EMMA trial (Essai Multicentrique Medicaments vs Angioplastie). This randomized

RAS = renal artery stenosis
FMD = fibromuscular dysplasia
ARAS = atherosclerotic RAS

BP = blood pressure

controlled trial enrolled 49 subjects with unilateral RAS to either angioplasty or medical treatment. The primary outcome measure was ABP (ambulatory blood pressure) at termination. Again, the results are unequivocal: "Mean ABP at termination and the average reduction in ABP between randomization and termination did not differ between groups." So, the authors conclude: "Previous uncontrolled and unblinded assessments of angioplasty overestimated its potential for lowering blood pressure."

Numerous other papers were published in the last decade. However, these three publications [8,15,16] were the only studies identified as randomized controlled trials qualified to be included in a meta-analysis published by Ives and colleagues a year ago [17]. They summarized the combined results to "exclude the possibility of a large improvement in renal function or hypertension after angioplasty," but speculate that a moderate benefit cannot be ruled out.

The Cochrane Collaboration published a review this year entitled "Balloon angioplasty versus medical therapy for hypertensive patients with renal artery obstruction" [18]. Here again, the only randomized controlled trials that met the inclusion criteria were the same three publications [8,15,16]. Not surprisingly, Nordmann and Logan, the authors, reached the same conclusion: "Angioplasty has not been shown to be more effective than drugs."

It is widely agreed that cure of hypertension caused by ARAS is an unrealistic goal in most cases; the reported rate is less than 10% [13,14]. However, in many studies, for a substantial number of patients the blood pressure is classified as 'improved' following angioplasty. I can only agree with Webster et al. [16]: "This classification is fraught with difficulties of definition, interpretation and the vagaries of regression to the mean." The reported "improvement" rate is about 36% [19] to 50% [20]. Even if this improvement is of clinical significance, it should be weighted against the considerable cost of this invasive procedure, in terms of complications. Webster and co-workers [16] report that 11 of 40 patients (27.5%) who underwent angioplasty suffered one or more serious or potentially serious complications directly attributable to the procedure. The rate of complications in the EMMA study was 26%. An analysis of pooled results in 1,118 patients [2] showed that 0.5% died in the hospital, 0.3% underwent nephrectomy, 2.0% required renal surgery, and 2.2% had occlusion of a side branch of the renal artery. Other reported complications include cholesterol embolization, rupture of renal artery, deterioration of renal function, and injury at the site of vascular access. Restenosis is another important issue that should not be ignored when considering PTRA. The rate of restenosis varies according to the site of the intervention (ostial vs. non-ostial lesion) and whether a stent was placed.

In summary, with regard to renovascular hypertension, on the one hand PTRA has not been shown to be more effective than drugs, while on the other, medical therapy alone is feasible for the vast majority of patients and there is a substantial risk of complications and restenosis. Taken together, the only logical conclusion is that at the present time PTRA should not be the primary form of treatment of renovascular hypertension due to ARAS. It should be considered as a reserve procedure for patients with severe resistant hypertension whose blood pressure cannot be controlled by medical therapy alone.

When ischemic nephropathy is the indication for PTRA, the aim of the intervention is salvage of renal tissue and prevention of end-stage renal failure. Crucial to this issue is the potential of the stenotic lesion to worsen over time. From recent studies [3] it seems that progression of ARAS occurs at varying rates. Zierler and colleagues conducted a prospective study on the natural history of ARAS in 76 subjects. Progression of RAS occurred at an average rate of 7% per year, by Duplex scanning [21]. Two years later the same group reported, based on the follow-up of 295 kidneys in 170 patients, a cumulative incidence of ARAS progression of 35% at 3 years and 51% at 5 years. However, only 9 of 295 kidneys (3%) progressed to occlusion [22]. Woolfson [23] quotes a reported rate of progression between 18% and 53% over a mean follow-up of 24–52 months. On the other hand, Leertouwer et al. [4], while performing digital subtraction angiography for peripheral vascular disease, identified ARAS in 126 of 386 patients (33%). None of these patients required renal replacement therapy during the 10 years of follow-up. Serum creatinine values remained stable during follow-up.

So, in different studies, the progression rate varies from 53% at 5 years to none at 10 years. This apparent contradiction highlights two important issues: One is the substantial difference in the population studied, in the diagnostic criteria and in the diagnostic tools used in the reported studies. The other is the gap between the imaging results [21,22] and the clinical reality, i.e., worsening of the stenosis by imaging criteria does not necessarily mean clinical deterioration.

In summary, at present the data in the literature are non-conclusive with regard to the actual rate of ARAS progression. However, it is possible to conclude with a good degree of certainty that most renal artery lesions do not progress rapidly [3]. There are ample reports on the results of PTRA for ischemic nephropathy [6,19,24]. In many publications, the authors categorize the results of the intervention as "improved," "stabilized" or "deteriorated." When pooling the reports, it is fairly accurate to assume that about 25% of the patients improved, 50% stabilized and 25% deteriorated. It should be remembered, however, that these terms lack precise definition. For example, in a recent report on PTRA with stent placement for ARAS (465 kidneys, 340 patients), Zeller et al. [7] used a 10% change in serum creatinine as the primary endpoint. Taking into account the many factors that influence the level of serum creatinine over time, the clinical relevance of a 10% change is unclear. Thus, they report a "statistically significant" ($P = 0.048$) decrease in Scr from 1.45 $\pm$ 0.87 to 1.39 $\pm$ 0/73 mg/dl, during a mean follow-up of 34 $\pm$ 20 months, while the small increase in glomerular filtration rate from 59 $\pm$ 26 to 62 $\pm$ 26 ml/min/1/73 m^2 did not reach statistical significance. The improvement rate of Scr

ABP = ambulatory blood pressure

PTRA = percutaneous transluminal renal angioplasty

Scr = serum creatinine

was 34%, while 39% were unchanged and 27% deteriorated (Scr increased by >10%). A Norwegian study (227 procedures, 135 patients) used quite different criteria: 20% change in Scr from baseline, when baseline Scr was 100 µmol/L (1.2 mg/dl) and a change of 20 µmol/L when baseline Scr was 100 µmol/L. Improved renal function was achieved in 23% of patients, stabilized in 56% and failed in 21% [19].

In uncontrolled trials, "stabilized" is a vague term that can be interpreted as success as well as failure of the procedure. Thus, the conclusion is that only in the minority of patients was PTRA undoubtedly successful in terms of salvaging renal function. Moreover, in almost the same percentage of patients not only was the goal not achieved but the renal function actually deteriorated.

Conclusion

At present there is no solid evidence that PTRA is superior to medical therapy for patients with ARAS. Thus, this procedure cannot be advocated as the primary treatment for these patients at large. It rather should be preserved for a subset of patients in whom aggressive medical therapy, aimed at all factors involved in the atherosclerotic process, was unsuccessful.

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Capsule

Disease and genetic variation

Although variations in the number of copies of individual genes in humans have been observed, a map of such variation would be important for genomic studies of disease. Sebat et al. used representational oligonucleotide microarray analysis (ROMA) to generate such a map and show that large-scale copy number polymorphisms are common and widely distributed in the human genome. The largest was over 2 megabases in size. In an analysis of 20 individuals from different geographic backgrounds, variation occurred at least once in 70 genes.

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