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Ischemic Nephropathy
More Than a Simple Renal Artery Narrowing

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Review

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Renal artery stenosis in elderly patients is mainly caused by atherosclerosis. The prevalence of this disorder in patients with chronic kidney diseases is reported to be 0.5% to 5.5%. However, because the patients with atherosclerotic renal artery disease are mostly asymptomatic, the true prevalence is expected to be higher. Renovascular hypertension and ischemic nephropathy are two main consequences of this disease, but it is difficult to determine in which patient the progress of stenosis may cause these syndromes. The big challenge in renal artery stenosis is how to manage the patients. In the past 70 years, it has been believed that simply maintaining of kidney perfusion by opening the stenosis could control blood pressure and preserve kidney function. Nowadays, the blood pressure can be controlled well by medical treatment without the need for revascularization; however, management of ischemic nephropathy remains a dilemma. With advancements in understanding the pathophysiology of changes in the parenchyma of the kidney after stenosis, it is now generally accepted that only a minority of patients with ischemic nephropathy will benefit from revascularization. Nonetheless, finding these patients is critical and need more randomized trials to show who mostly benefit from revascularization and when it may save the kidney.

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INTRODUCTION

Atherosclerotic renal artery stenosis (ARAS) is the most common primary renal artery disease that causes two different disorders, renovascular hypertension and ischemic nephropathy.[1-5] Atherosclerotic renal artery stenosis is a common cause of end-stage renal disease (ESRD) in elderly patients, and approximately 10% to 20% of ESRDs are due to ARAS among patients older than 50 years.[6,7] The prevalence of ARAS is increasing day by day, which may be due to the better control of other vascular diseases that results in longer survival in communities.

Atherosclerosis is a systemic disease and 90% of renal artery stenosis cases are due to this disorder.[8] Atherosclerotic renal artery stenosis is one of the most important causes of accelerated hypertension; nevertheless, at the same time it is one of the most common vascular diseases that can accidentally be discovered. Jacobson proposed in 1988 the term *ischemic nephropathy* (IN) to refer to impaired kidney function due to renal artery stenosis.[9] In patients with ARAS and significant reduced glomerular filtration rate (GFR), IN should be a differential diagnosis, but the term IN is only applicable if the entire mass of the kidney is affected by ARAS (bilateral ARAS or stenosis in a single functioning kidney), and thus impaired kidney function in unilateral renal artery stenosis means that other parenchymal diseases are present.

Ischemic nephropathy is potentially a reversible kidney failure, but because of the progressive nature

of the disease, it may lead to ESRD, too. In the past decade, dramatic advances in imaging techniques in addition to the advantages of medical treatment of hypertension and methods of revascularization changed the issue of ARAS. Despite these progresses and perhaps because of these developments, many controversies about the management of ARAS raised among the interventionalists and nephrologists. With recent advances in vascular intervention, finding a narrowing of the artery is tempting to open it. On the other hand occasional reports that renal arteries revascularization improve the kidney function is considered as a document that all renal artery stenosis should be revascularized as well.

EPIDEMIOLOGY

Atherosclerotic renal artery stenosis is an aging disorder and population studies show that significant ARAS (> 60% stenosis) is common in elderly patients, and men are affected more than women (5.5% versus 1.9%, respectively).[10] Demographic characteristics of patients with ARAS have changed dramatically within the past 50 years.[11] The age of these patients has been increased from 50 to 60 years to 70 to 80 years, and many of these patients are suffering from other comorbidities. The real prevalence of ARAS is unclear, because the disease is often asymptomatic and there is no general screening plan for these patients unless they have symptoms or known risk factors. On the other hand an acceptable definition of ARAS is not determined (stenosis only or in combination of reduced GFR or hypertension), and finally various detection methods with different sensitivity and specificity obscured the exact prevalence of disease. However, it is more likely that the prevalence is much higher than being now reported. The more difficult issue is the prevalence of IN. It is very difficult to determine whether the chronic kidney disease (CKD) is due to ARAS because many patients with CKD do not undergo angiography, fearing of contrast nephropathy. However, many reports showed that the prevalence of the disease is increasing.[12-14]

In autopsy studies, the prevalence of the ARAS has been 4% to 50%, depending on age[15-17]; 5% of people younger than 64 years, 18% within 64 to 74 years, and 42% of those over 75 years had had ARAS. In an epidemiological study including more than 1 million people in the United States, the incidence of ARAS was 0.39% per year in people over 65 years and the prevalence was 0.5%.[13] Autopsy of patients who died of stroke showed that 10.4% of patients had ARAS with more than 75% stenosis. There is also correlation between ARAS and carotid involvement.[18] Forty-six percent of the patients with ARAS had carotid disease, while only 12% of the patients without ARAS had carotid involvement.[19] It is presumable that the percentage of patients with ARAS who are diagnosed during life is much less, so it can be concluded that the ARAS is a clinically silent disease. Hansen and colleagues have shown that 6.8% of elderly asymptomatic patients have ARAS (> 60% stenosis).[10]

According to the Dutch Renal Artery Stenosis Intervention Cooperative study,[20] age, symptomatic cardiovascular disease, high blood cholesterol level, and abdominal murmur are strong predictive factors of ARAS (> 50% stenosis). In a large multicenter study in Spain, the average age of patients was 68.7 and the ARAS was more common in men. More than 97% of the patients had hypertension. Smoking and hypercholesterolemia were evident in 69.8% and 62.9% of patients, respectively. Eighty-two percent of patients had other vascular involvements, and the peripheral vascular disease was the most common form (65%).[21] In magnetic resonance angiography studies, 34% of patients over 70 have ARAS (> 50% stenosis). In these patients, peripheral artery disease and higher serum creatinine were more common.[22]

Atherosclerotic renal artery stenosis is a component of a systemic process. Thus, it is not surprising to be detected at the time of other vascular evaluations. The prevalence of ARAS detected by angiography is 11% to 42%. The prevalence is higher if the patients have at least one of the following risk factors: severe hypertension, CKD of unknown cause, acute pulmonary edema, and severe atherosclerosis; it was shown that 39% of patients with these condition had ARAS, but stenosis greater than 50% and 70% were found in 14.3% and 7.3% of these patients respectively.[23] The prevalence has been increasing in cases with generalized atherosclerosis, peripheral vascular disease, and aortic disease.[24,25] Some degree of renal artery stenosis was found in 47% of hypertensive patients who underwent coronary angiography. Among them, 19.2% had ARAS of more than 50% stenosis, 7% of more than 70% stenosis, and 3.7%

bilateral stenosis.[26]

Patients who have advanced peripheral atherosclerosis and involvement of the aorta or the lower limb have the greatest likelihood of ARAS (35% to 50%).[26-28] In a study of patients who had coronary angiography, the prevalence of ARAS was 11%, and 4% had bilateral ARAS.[29] Two-third of these patients had severe coronary stenosis. In other words, patients with coronary artery disease have a 55% increased risk of having ARAS, while less than 10% of individuals with normal coronary have ARAS.[29,30] Sixty-seven percent of patients with ARAS may have concurrent coronary artery disease. This proportion for peripheral vascular disease and cerebrovascular disease are 56% and 37%, respectively.[13] Interestingly, the prevalence of these diseases was 2 to 4 times more in those who had ARAS than those who had a normal renal artery. Zoccali and colleagues showed that 39% of patients with aortic aneurysm, 33% of patients with aortic occlusive disease, and 39% of patients with lower limb peripheral artery disease had ARAS with more than 50% stenosis.[31] In another study, about 45% of patients with peripheral vascular disease had ARAS.[32] In a third study, 48% of people who had aortoiliac disease had ARAS, among whom 26% had stenosis of more than 50% and 21% more than 70%.[33] The prevalence of ARAS is also high in patients with congestive heart failure; 34% of these patients have significant ARAS.[34] While nonsignificant ARAS is seen in 66% of these patients,[35] flash pulmonary edema may occur in 10% of patients with ARAS and it may be a primary clinical manifestation of this disorder.[36]

End-stage renal disease is more likely to be due to ARAS in older men without a known cause of the CKD. Blacks, Asians, and Native Americans are less affected by this complication. It has been reported that the incidence of ARAS as a cause of ESRD has increased from 2.9 to 6.1 per million people, between 1991 and 1997.[37] It is speculated that 5% to 14% of patients with ESRD who are older than 50 years have ARAS as the cause of the kidney disease.[38-40] In another study on patients with ESRD, the prevalence of ARAS was estimated to be 15% and it would increase to 25% as age increased.[41]

Ischemic nephropathy is a major cause of ESRD in patients older than 65 years. Twelve percent of patients with bilateral ARAS progress to ESRD. The GFR declines by 8 mL/min each year on average.[42] In one study, the incidence of ESRD due to IN was associated with 12.4% annual increase, which is more than the increase in diabetes mellitus rate (8.4%) and ESRD of all causes (5.4%).[37] Jacobin and coworkers showed that 41% of the patients who started dialysis at the age of 45 years or greater were diagnosed with ARAS. The ratio of women to men was 2:1 and 16% had bilateral stenosis. There was no evidence of risk factors of ESRD rather than hypertension.[43]

However, the question remains that how much renal artery stenosis causes significant kidney failure? Almost all the patients have hypertension and it appears that high blood pressure has a more important role in ESRD than ARAS. Only 2% to 5% of hypertensive patients have ARAS, while approximately 90% of ARAS patients have high blood pressure. In other words, the probability that the CKD is due to essential hypertension is more likely than to be due to ARAS. Thus, it can be concluded that ARAS is not clinically significant in these patients. On the other hand, the prevalence of ARAS is also high in patients with CKD (3.2% of patients younger than 59 years and 25% of patients older than 70 years).[44] At least 2.1% of ESRDs are due to ARAS in the hemodialysis population.[37,45] These patients are more susceptible to cardiovascular diseases and deaths.[12]

CLINICAL COURSE

Atherosclerosis is generally a progressive disease. Progression of stenosis, renal atrophy, and complete obstruction of the renal artery in one year are estimated to be 20%, 10%, and 5% respectively.[46,47] The rate of progression is related to the extent and severity of systolic blood pressure and other risk factors. Meanwhile, it has not been confirmed whether the severity of stenosis plays a role in kidney function loss. Up to now, no unique endpoint has still been defined to assess the disease progression.[48] Some endpoints have been used, but more investigation is needed to find surrogate markers of progression. These can be the size of the kidney, GFR, and diameter of the stenosis.

Anatomical Progression

It seems that progression of stenosis is dependent on the severity of the primary lesion. Within 2 to 5

years, 25% to 75% of patients with stenosis of more than 25% may have progress. The risk of complete occlusion is 8% to 16%. Complete obstruction of the artery is usually seen in patients who have more than 60% stenosis at the time of diagnosis. It is also more common in patients with bilateral stenosis. At least 16% of these patients will have complete occlusion within 1 to 5 years.[49]

In a study on patients who had cardiac angiography, ARAS (> 50%) was found in 2.4% of the patients. Following up of these patients for an average time of 2.6 years showed that the rate of stenosis increased to 13.5%. One decade later in a duplex Doppler study, these results were confirmed.[50] In another Doppler study in which the patients were followed up 3 years, it was found that the incidence of progression was 18% in patients with a normal renal artery, 28% in those who had stenosis of less than 60%, and 49% in patients who had more than 60% ARAS at beginning. In this study, the risk of complete occlusion was low.[48] Some studies with 6 to 180 months follow-ups did show that the stenosis would progress in 50% of patients within 5 years.[40] The rate of progression would be varied from 1.5% to 5% each year,[49,51] and possibly most of the progression would happen in the first 2 years after diagnosis.[49]

Progression to complete occlusion occurs in 15% of patients.[49,50] The more severity of stenosis the greater risk of total occlusion; 39% of patients who have stenosis of more than 75% are likely to have complete obstruction within 13 months.[49] In a study with duplex Doppler documentation, progress of ARAS was 35% and 51% at 3 and 5 years, respectively.[48] Nonetheless, this also means that 50% of patients have no progression at 5 years. In this study, the possibility of complete renal artery occlusion was less than 3%. All occlusions occurred in those with more than 60% stenosis from the baseline. It was assumed that other than the severity of stenosis, the systolic blood pressure and diabetes mellitus are the other predictive factors of progression.[48] It was also shown that the rate of progression in 3 years was 28% and 49% in ARAS patients with less or more than 60% stenosis, respectively. The rate of progression was only 18% in patients with normal renal artery at baseline.

Atrophy of Kidneys

Atrophy of the kidney is a main complication of progression of ARAS. Reduced kidney size or atrophy may be a better indicator of progression of ARAS. If kidney atrophy can be attributed to the reduced renal blood flow, changes in the kidney size over time will therefore be a good and reasonable criterion for evaluation of stenosis progression. There are a few reports about these changes in the literature. In a study in which the patients were followed up for 6 to 48 months, 37% of the patients had 10% changes in their kidney size. Meanwhile, a 30% reduction in GFR has been documented in 25% to 50% of these patients.[52] In another study, 44% of patients showed disease progression, and 70% of these patients showed more than 1.5 cm reduction in the kidney size.[49] Finally, in a study with a criterion of more than 1 cm reduction in the kidney size, the variation of progression over 33 months was different according to the baseline stenosis; 5.5%, 11.75%, and 20.8% in patients with normal renal artery, less than 60%, and more than 60% stenosis respectively.[46]

Functional Progression

Reduction in GFR may be a useful determinant for progression of IN. It should be noted that it is not as sensitive as either stenosis progression or atrophy, particularly if serum creatinine is chosen as a marker of kidney function. Comparing patients with and without ARAS, a 10 years' follow-up showed that although the baseline serum creatinine was 20% more elevated in the ARAS group, it was remained stable during the follow-up period. None of the patients in either of the groups progressed to ESRD.[53] In another study, patients with ARAS (> 70% stenosis) were followed up for 39 months. Less than 12% of the patients had functional progression leading to either kidney failure or the need for revascularization. About 60% of the patients had a stable serum creatinine at a maximum level of 1.3 mg/dL and had only mild hypertension.[54] It has been shown that the severity of ARAS is not correlated with the severity of kidney failure.[55] It is more likely that the decrease in GFR in the course of the ARAS is not related to lesions of the greater arteries, but there is a good relation between GFR and the multifactorial parenchymal lesions which are prominent in the tissue after stenosis. Considering all these studies, it seems that the best predictive factors for progression of ARAS to ESRD are GFR

and renal atrophy, and renal artery diameter is less important.

SURVIVAL

In the presence of ARAS, if the GFR is low, survival is poor, regardless of whether or not the patient undergos revascularization. The main cause of the high mortality rate is cardiovascular events.[56] Although the relationship between ARAS and progressive loss of GFR is controversial, the relationship between GFR and survival is clear. The average life expectancy is 2 years, and the 5- and 10-year survival rates are 18% and 5%, respectively. The average life expectancy of patients with polycystic kidney diseases is 11 years and their 5- and 10-year survival rates are 77% and 59%, respectively.[24] Another study demonstrated that the 4-year survival of patients with and without ARAS was 65% and 86%, respectively.[57] Kennedy and colleagues showed that the ARAS patients with 75% stenosis had 89% survival within 4 years, while the survival was reduced to 57% in patients with more than 75% stenosis.[56] It has also been shown that the life expectancy of dialysis patients who have ARAS is less than those without ARAS.[58]

Kidney function and serum creatinine level at the time of diagnosis are important factors in predicting survival of these patients. Even if these patients can be successfully revascularized, the rate of cardiovascular death will not be reduced. Those who have mild to moderate decrease in kidney function and worsening of kidney function after revascularization have the greater risk for cardiovascular complications (31% versus 19%), but in patients with moderate to severe kidney function impairment who remain stable after the procedure, the cardiovascular risk is significantly less than those with further reduction in GFR (50% versus 23%).[56]

This high rate of mortality associated with ARAS is related to the pathophysiology of this disease.[59] In a study by Cha´bova and associates,[60] the patients were followed up for both blood pressure and serum creatinine. The authors showed that the changes in blood pressure were not significant. Meanwhile, in a small number of patients, serum creatinine level increased (in 10 of 68 patients, 6 of whom reached ESRD). All these patients had bilateral ARAS or stenosis in a solitary functioning kidney. These 10 patients had a high mortality rate (42.9% versus 21.3%). Looking at the age of these patients (mean, 78 years), it seems that death has happened independent of kidney function and it is not known that interventional measures can reduce this rate. Based on this study, perhaps it may be concluded that only a very small percentage of patients benefit from interventional measures.

Comparison of the ARAS group with other populations shows that the rate of death is higher than that in patients with angina pectoris, equal to those of colon cancer.[61] Some studies have attempted to identify characteristics that may predict survival of these patients. The predictive factors of death in patients with ARAS and hypertension include older age, kidney failure, and bilateral ARAS.[61] Angiotensin-converting enzyme (ACE) genotype is another predictor. The DD genotype, which is a deletion polymorphism, is associated with a higher risk of cardiovascular and kidney diseases.[62] In this condition, the activity of the renin angiotensin system is higher than normal and the rate of death is doubled in patients with ARAS.[63]

Generally speaking the risk of death in patients with ARAS is 6 times higher than the risk in those who are at risk of progression to ESRD.[12] Paradoxically, one study has shown that the risk of ESRD or death in patients having nonsignificant ARAS is higher than those who have significant ARAS (odd ratio, 3.39 versus 0.95).[64] Further studies are needed to interpret these findings.

CLINICAL SYNDROMES

The clinical features of ARAS are very diverse and they may be varied from asymptomatic to stroke and heart failure resistant to treatment. Probably, most of these patients are asymptomatic and may be accidentally discovered. One of the most important issues that the physician should evaluate is the relationship between ARAS and cardiovascular disease. For instance, when blood pressure surges suddenly in a stable patient or when a sudden stroke with no specific cause happens, ARAS should be on the top of the differential diagnosis list. These complications are seen mostly in patients with bilateral ARAS associated with the underlying heart disease.

The most important clinical syndromes of IN are listed in Table 1. Mild proteinuria is not uncommon, but nephrotic proteinuria has also been reported. The severity of proteinuria is a marker of renal

Table 1. Clinical Syndromes Associated With Atherosclerotic Renal Artery Stenosis

Clinical Syndromes
Mild proteinuria
Occurrences of sudden hypertension
Progressive kidney failure associated with hypertension
Hypertension associated with retinopathy grade 3 (25% to 40%)
Kidney failure of unknown cause associated with hypertension
Kidney failure of unknown etiology associated with hypokalemia
Kidney failure without known cause associated with flash pulmonary edema
Kidney failure associated with coronary artery diseases or peripheral vascular diseases
High blood pressure associated with signs of diffuse atherosclerosis in men over 60 years
Acute kidney failure after taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers
Idiopathic renal insufficiency and hypertension associated with murmur on the epigastria and femoral artery

parenchymal damage in IN, and it will be reduced after revascularization and reduction of the level of angiotensin, if it is due to ARAS.[65,66]

PATHOPHYSIOLOGY

The term "ischemic nephropathy" itself indicates what exactly is going on in the kidney, and it generally refers to renal insufficiency due to main renal arteries stenosis.[67] However, it does not necessarily reflect that only ischemia is playing a role. The main work of the kidney is filtration and the supply of renal blood flow is much more than demands of the kidneys. It is known that only 10% of blood supply is enough for kidneys to work perfectly.[68] If the perfusion pressure of the kidneys fall down to 40%, the renal blood flow and the GFR will not change due to autoregulation mechanism.[69] Further reduction in perfusion pressure is associated with mildly reduced GFR and renal blood flow. It has been shown that 70% to 80% stenosis of renal arteries cause about 40% reductions in perfusion pressure.[70] For these reasons, the renal atrophy and fibrosis is not justified by decreased renal blood flow and low tissue oxygenation per se.[14] Although a number of ESRD cases do not have any causes other than ARAS, many studies in this regard imply that a complex interaction between stenosis, vascular damage, blood pressure, and organ damage are in operation. The actual mechanism of kidney damage in IN, however, is not well characterized. It is shown that a more severe stenosis is associated with more severe kidney dysfunction, but it can be concluded that these patients have been affected by the process of atherosclerosis for longer time.[71] Thus, some authors used the term of chronic *renovascular azotemia* instead of IN.[72]

The pathways of tissue damage in ARAS are not known clearly. In fibromuscular dysplasia, despite severe stenosis there is no tissue damage. Fibromuscular dysplasia can make endothelial changes, but after revascularization, all these changes recover. Fibromuscular dysplasia is not associated with other vascular diseases and the risk factors of atherosclerosis are absent. It may be concluded that the stenosis per se is not a strong enough stimulator for the tissue damage seen in ARAS. In atherosclerosis, declining of GFR is due to many known and unknown mechanisms that cause multiple layers of microvascular injury leading to tissue damage and fibrogenesis.[73]

Hemodynamic studies show that changes in renal blood flow occurs when 70% to 80% of the vessel lumen is affected. This condition is called "critical stenosis.[74]" There should be a link between reduced perfusion pressure and ischemic pathways. Some experimental studies showed this relation.[75] Based on the study of Chade and colleagues, the endothelial response to vasoactive agents is inappropriate and causes overproduction of isoprostane that is an oxidative stress marker.[76] Atherosclerotic renal artery stenosis can activate vasopressor systems, for which the rennin angiotensin is the axel. Both angiotensin II and its by-product endothelin 1 induce vasoconstriction to maintain blood flow after stenosis. Lowering blood pressure in this condition beyond the autoregulation properties may contribute to further GFR reduction.[77] Theoretically, revascularization causes the GFR to operate independently of pressure.[74,78]

Today, it is clear that the angiotensin has a greater effect than blood pressure modulation on

ARAS. Vascular and myocardial remodeling and expression of the tissue growth factor-β (TGF-β) gene and platelet derived growth factor-β (PDGF-β) mRNA in the intrestitium are well known. These factors cause increases in extracellular matrix and collagen IV, the role of which in tissue damage is well characterized.[14] Thus, inhibition of this system has many effects beyond the blood pressure control. Shortly after occurrence of stenosis, the pressor mechanisms of oxidative stress are playing their role.[75] High-cholesterol diets are associated with higher activity of these mechanisms. Then, the fibrogenic cytokines are expressed in the kidney. They in turn activate the TGF-β and nuclear factor kappa-light-chain-enhancer of activated B cells.[79] Parenchymal scarring due to these changes is now going on independent of ARAS and it will remain active despite revascularization. From this perspective, the use of antioxidants is justified.[80] However, it appears that both vasoactive factors and fibrogenic mechanisms are operating hand in hand and treatment one pathophysiologic arm may not be so effective.

In recent years, the inflammatory mediators are at the center of attention. Among them, free radicals of oxygen, reperfusion injuries, and matrix modulation are more attractive for describing the tissue damage in ARAS. The role of oxidative stress is partially known.[81] Oxidative stress refers to a condition that causes tissue damage due to increased oxygen free radicals.[82] Oxygen free radical scavenges nitric oxide and reduces tissue oxygen pressure. This condition in association with stenosis has many consequences on endothelial and epithelial cells. They also augment the vasoconstrictor effect of angiotensin II, endothelin 1, adenosine, and norepinephrine. Animal studies show that inhibition of oxidative stress can control blood pressure.[83,84] Previous animal studies have also shown that antioxidant vitamins inactivate the fibrogenic pathways including nuclear factor kappa-light-chain-enhancer of activated B cells and TGF-β.[85] Considering all these studies, we can conclude that the activation of oxidative stress is a major pathway of hemodynamic changes and hypertension as well as kidney failure.[83,85,86]

Although blockade of oxidative stress pathways may halt the tissue damage, it cannot stop the process. This means that there are other pathophysiologic mechanisms rather than hemodynamic and oxidative stress. An important pathogenic factor in ARAS is oxidized low-density lipoprotein that is known as a vasoconstrictor agent. Reactive oxygen species facilitate oxidation of low-density lipoprotein, signaling growth factors. Cytokines like PDGF and TGF-β are promoted by reactive oxygen species, too.[87,88] Reactive oxygen species also inhibits degradation of extracellular matrixes while it induces other profibrotic factors.[89]

The other mechanism involved in IN is reperfusion injury.[90] Initial damage due to ischemia may exacerbate during reperfusion, mediated by reactive oxygen species in an inflammatory cascade. Hypoperfusion and congestion of outer medullary continue, despite the recovery of cortical blood flow, cause worsening of preexisting hypoxia, which leads to prolongation of tissue damage and even cell death. Endothelial damages are playing an important role in hemodynamic changes.[91] Activation of mitochondrial enzymes and changes of mitochondrial membrane potential eventually lead to apoptosis. In addition to these harmful changes, low tissue oxygen tension is a known stimulant of protective mechanisms such as increases in adrenomodullin and hypoxia-inducible factor 1 both in vitro and in vivo.[92,93]

Scar formation and remodeling are dynamic processes working together for simultaneous synthesis and degradation of extracellular matrix. This balance may be interrupted in some processes such as ARAS. These synergistic complex mechanisms may explain why revascularization has no or little effect in preventing kidney failure in ARAS.

By scar formation, tissue circulation further deteriorates and causes more tissue damage. However, recently it has been shown that even in the early stages of the disease, yet there is no scar tissue, there is an imbalance between oxygen supply and demand.[94] It has been reported that the GFR in the contralateral kidney with a normal renal artery is the same as or even lower than the GFR in the stenotic kidney. It means that kidney failure is going on independent of ARAS and some other factors including hypertension are independent factors contributing to kidney failure of ARAS patients.[95]

Proteinuria, a key marker of the renal damage in patients with ARAS has a strong direct relationship between baseline kidney function and eventual

kidney failure and patient survival.[96,97] Finally, the risk of thromboemblism is high and up to one-third of renal blood supply may be affected by this phenomenon.

In summary, although our understanding of the pathophysiology of ARAS has improved and we know that ischemia and inflammatory and fibrogenic factors are operating hand in hand, still we have to wait to find better diagnostic and therapeutic avenues for this disease. The high death rate in these patients is due to this complex pathophysiology of the disease.[59]

SCREENING AND DIAGNOSIS

The purpose of diagnosis of ARAS is to prevent the main side effects of the disease. This includes blood pressure control (complete remission or reduction of antihypertensive medications) and also attempts to stop or delay the progression of kidney failure. Thus, evaluation of these patients includes tests to show renal anatomy and function. Showing a stenosis in the renal artery does not mean that it is a clinically important finding, and more studies should be performed to see if ARAS in a particular patient is responsible for decreased GFR.[9] The ideal test is the one that is easily available, noninvasive, nonnephrotoxic, and able to show the anatomy of renal artery as well as the functional value of the stenosis. If a diagnostic method is able to show that whether or not the intervention is beneficial, it is excellent.[98]

In hypertensive patients, there is no need for extensive evaluations unless the secondary hypertension is suggested by primary tests.[99] Some investigators perform peripheral angiography during coronary angiography in patients with atherosclerosis diseases.[100] However, the main question is while incidentally discovered ARAS will not change the management plan of these patients, what the cost-benefit ratio of this procedure is.[101,102]

The gold standard for diagnosis of ARAS is renal angiography, but several noninvasive tests are available for screening.[103] The main problem with all these tests are their high false negative values (low sensitivity), and therefore, many patients with ARAS may remain undetected.

For detection of anatomical abnormalities of the renal arteries, there exist spiral computed tomographic (CT) angiography, magnetic resonance imaging (MRA), and conventional angiography, while for evaluation of kidney function, color duplex Doppler ultrasonography and isotope scanning with ACE inhibitors are useful.

Ultrasonography

Ultrasonography is the first step to evaluate the size, symmetry, and architecture of the kidneys. It is the best tool for assessing renal parenchymal echogenicity. More than 15 mm differences in size of the kidneys is suggestive of ARAS, but it can also be seen in other diseases like focal segmental glomerulosclerosis. Equal size of the kidneys cannot rule out the ARAS. The size of the kidneys is an important factor to make decision for revascularization. Revascularization of the kidneys less than 80 mm is not indicated.

Duplex Doppler Ultrasonography

Duplex Doppler ultrasonography is inexpensive, available everywhere, safe, and highly sensitive and specific. It can reveal both the anatomy of arteries and the functional importance of ARAS. Due to the limitations of this test related to both patients and the operator, different values for sensitivity and specificity have been reported (sensitivity, 63% to 100%; specificity, 73% to 100%).[104] On average, its sensitivity is 85% and the specificity is 92%,[105] but in the hands of a skilled radiologist in a well-equipped center, both the sensitivity and specificity are more than 96%. Doppler ultrasonography can determine the resistive index, may evaluate the small vessel of the kidney, and is able to assess the renal parenchyma. Resistive index is an indirect sign of fibrosis or atrophy of the kidney. There is a direct relationship between resistive index and histopathology changes.[106] A resistive index greater than 0.80 indicates that revascularization has no benefit in improving the kidney function. Resistive index is reduced in the ARAS, so lower values in these patients does not necessarily mean that the parenchyma has been preserved. The advantage of Doppler ultrasonography is that its sensitivity and specificity have no relationship with the level of GFR. Disadvantages of this approach include: (1) it is time-consuming (it may take up to 2 hours); (2) the quality of work is dependent on the patient body weight and bowel gas; (3) it is dependent on the operator's level of skill; and (4) minor vascular and aberrant vessels are rarely identified. Considering all these benefits and

limitations, the duplex Doppler ultrasonography is the first screening method of patients suspected as having ARAS, if a skilled radiologist performs the test.[107]

Spiral Computed Tomographic Angiography

Spiral CT angiography is a very accurate noninvasive method for screening of ARAS. Its sensitivity and specificity for detection of a stenosis greater than 50% are 64% to 99% and 92% to 98%, respectively,[108,109] but by using the maximum-intensity projection techniques and 3-dimensional method, the sensitivity may increase to 98%. Spiral CT angiography shows renal artery anatomy and cannot tell that whether revascularization has benefit or not.[110] Its advantage over conventional angiography is that it can visualize both arterial lumen and arterial wall. Its main disadvantage, like conventional angiography, is the use of iodine contrast material.

Magnetic Resonance Angiography

Magnetic resonance angiography is a noninvasive procedure using gadolinium as contrast medium. In centers not expert with Doppler, the MRA is becoming more popular. Its sensitivity for detecting major renovascular lesions is 100% and the specificity is 96%.[111] The sensitivity and specificity of this technique in ARAS with stenosis greater than 50% are 97% and 93%, respectively. Without 3-dimensional method, these rates are 94% and 85%.

Recently, the simultaneous phase contrast MRA and MRA is used to evaluate the functional importance of stenosis and has had promising results,[112] but for now, MRA has no role in determining whether or not the patient is benefiting from revascularization. The main problem with MRA is the exaggeration in intensity and degree of stenosis. Three-dimensional MRA increases the specificity. Another drawback is that it cannot be used in patients having metal or pace maker in their body or those who have claustrophobia. Magnetic resonance imaging also has no power to assess stented vessels. Another problem with MRA is the occurrence of nephrogenic systemic fibrosis in patients with severe kidney failure, although it has been claimed that the newer cyclic gadolinium is safe.

Comparing with Doppler ultrasonography, MRA has a higher sensitivity and a higher negative predictive value, but the specificity and positive predictive value of these methods are comparable.[113,114] A meta-analysis has shown that among different methods of screening of ARAS, CT angiography and MRA are the best, but both can only determine the anatomy of the arteries.[115]

Conventional Angiography

Despite numerous complications, conventional angiography is still the gold standard for diagnosis of ARAS. However, because of these complications, it cannot be used as the screening method for detecting the ARAS and it should be reserved for a definite diagnosis of ARAS or when the intervention is applicable.

Scintigraphy With Angiotensin-Converting Enzyme Inhibitors

Sensitivity and specificity of scintigraphy in high-risk patients is more than 90%,[116,117] but if the GFR is reduced, its value would be questioned.[118] Nevertheless, it is an appropriate screening test in patients with normal kidney function. In patients with moderate renal failure (GFR > 50 mL/min), the sensitivity of 86% to 87% have been demonstrated,[119,120] while other studies have shown a maximum sensitivity in these patients to be 75%.[121] The advantage of this test is that it can determine the functional importance of the stenosis independent of the anatomy of the renal arteries. Its limitation is that the patient should be prepared well before. For instance, 72 hours before scanning, effective drugs on the rennin angiotensin system should be discontinued.

In addition to renal failure, in bilateral renal artery stenosis or stenosis of single kidney, the value of the test is low. Nowadays, the most applicability of scintigraphy is to show the feasibility of the silent kidneys. It is a good tool to evaluate the function of each kidney separately and if the GFR is low there is no logical way for revascularization.

In summary, the screening test for ARAS should be chosen depending on the center capabilities (center facilities and operator's skill). In patients with a GFR greater than 50 mL/min, the function of the kidneys should primarily be evaluated by ACE inhibitor renography. In patients with a GFR less than 50 mL/min, Doppler ultrasonography or MRA with cyclic gadolinium can be used and

the first study should assess the anatomy of renal arteries. In patients with kidneys sized less than 8 cm or with a resistive index greater than 0.80, no further evaluation is recommended because there is no option for interventional treatment for these patients.

There are still plenty of debates around the role of renal angiography as a screening test during coronary angiography. Some tend to do that and believe that ARAS is a common comorbid condition in patients with coronary diseases and there is no need to additive facility to perform simultaneous renal angiography.[121] They say that the presence of ARAS and its severity are independent risk factors of death in these patients.[54] Some believe that ARAS accelerates hypertension and interfere with the primary and secondary preventive measures of coronary diseases,[121] and finally, the CKD due to ARAS will affect the outcome of both coronary angioplasty and coronary artery bypass. The oppositions of simultaneous coronary and renal angiography argue that if a significant stenosis is detected by such measures, its clinical significance is under question and there is no relation between the severity of stenosis and the GFR.[122] Otherwise, the medical treatment of hypertension is effective and safe and there is no need for intervention in most of these patients.[121] They consider the complications of these procedure that may outweigh their benefit.

TREATMENT

Management of ARAS is one of the few disputed issues between different specialty areas. Up to now, cardiologists and radiologists have been in the forefront of treating these patients. They tend to do interventional measures, so detection of stenosis anywhere in the body provides a golden opportunity to them to open it. The thought is that this measure can save the organ, and in the case of ARAS, hypertension will be cured and it reduces the possibility of heart failure resistant to treatment. Until 15 years earlier, nephrology literature would support the idea, but during the past 15 years, it has been completely changed, and management of this disease is now different. Unfortunately, patients are referred to nephrologists when the interventional procedures have been performed, mostly because of the complications of revascularization including more renal loss. Although ARAS is a progressive disorder and may cause complete obstruction, decision to revascularize the patient should be made after evaluation of associated diseases. Follow-up of patients with incidentally discovered ARAS has shown that although they may have severe kidney failure, their mortality is related to cardiovascular diseases rather than the kidney failure.[96] There is no doubt that some patients with ARAS will lose their kidney function over time, but there is also no doubt that many of these patients are diagnosed accidentally and the ARAS has little hemodynamic effects. There are no studies to show which of these patients will benefit from revascularization.

Medical Treatment

All IN patients have many other diseases and risk factors and should take many medications. These treatments have tremendous effect in reducing the mortality due to coronary artery and cerebrovascular diseases. This mortality reduction may be a main cause of increment in incidence of IN.[27] Efforts should be done to prevent atherosclerosis progression. Control of blood pressure and treatment of hyperlipidemia is the main cornerstone of such efforts. Use of antiplatelet drugs, smoking cessation, lifestyle modification, exercise, and less salt consumption are the other meausres to halt atherosclerotic processes.

The efficiency of ACE inhibitors and angiotensin receptor blockers on blood pressure is so high that nearly in all ARAS patients with hypertension, the blood pressure may easily be controlled without needing interventional measures.[59,123,124] Before the era of ACE inhibitors, blood pressure was controlled in less than 50% of the patients. This proportion is now much higher.

It has been suggested that kidney failure is one of the indications of using ACE inhibitors. Mann and colleagues compared the mortality rate in patients with vascular disease and mild kidney failure with those with normal kidney function. They showed significant increase of mortality in the first group which was independent of known cardiovascular risk factors.[125] In this study, inhibition of the angiotensin system reduced the death rate. However, whether ACE inhibitors reduce the rate of stenosis progression needs further studies.[126]

Revascularization

Endpoints of revascularization in different studies include blood pressure, kidney failure progression, mortality, and renal arterial patency. Because almost all ARAS patients suffer from other diseases such as diabetes mellitus, congestive heart disease, cerebrovascular disease, coronary artery disease, and CKD, it is very difficult to assess these endpoints as surrogate markers of ARAS.

Revascularization and medical treatment have been compared in terms of blood pressure control and maintaining the renal blood flow. The Dutch Renal Artery Stenosis Intervention Cooperative study is the largest of its kind with a total of 106 patients recruited.[127] Three months after randomization, blood pressure was similar in both groups although the number of medication significantly reduced in revascularization group. In addition, GFR was higher in this group. Half of the patients in the medical treatment group were revascularized sometime during the follow-up. Blood pressure significantly improved in these patients, but the GFR did not change significantly. Finally after 12 months, both groups had similar blood pressure and kidney function. According to this study, angioplasty has little benefit over medical treatment except in cases of refractory hypertension or progressive azotemia.

Generally, the effect of revascularization on survival of patients has not been established.[57,128] Retrospective studies have failed to show that revascularization could increase patient survival, but if it controls blood pressure, the patients may have better survival.[60] The effect of revascularization on kidney function is much more controversial. One study showed that patients without intervention had a slight decrease of GFR within 8 to 9 years of follow-up and none reached ESRD.[51] A meta-analysis revealed that despite the elimination of stenosis by angioplasty, there is no improvement in kidney function.[129] But it should be noted that if some patients do not benefit from such modalities, it does not mean that no patient would benefit from revascularization. It is now clear that only certain but few patients with ARAS have indications for revascularization. Baseline serum creatinine level is one of the important factors that will determine who will benefit from revascularization. The higher serum creatinine level the less favorable prognosis and no benefit from revascularization.[52,56]

In a series of patients with serum creatinine levels over 2 mg/dL who underwent revascularization, 27% had significant improvement in serum creatinine, and although the majority of patients (52.6%) showed no change in their serum creatinine, it was likely that these patients had little risk of progression.[71] However, no change in the mean serum creatinine values means that some of these patients rapidly deteriorated (20%), so the cumulative results of patients was misleading.[71] In total, it is presumed that the patients with serum creatinine levels higher than 3 mg/dL have very little chance of recovery after revascularization.[130,131]

In addition to kidney function, some other factors may be helpful in decision making about revascularization (Table 2). In all these patients, however, if the resistive index is more than 0.80 and the size of kidney is less than 8 cm, the chance to control blood pressure or to preserve or improve kidney function by revascularization is very low.[107] Flash pulmonary edema is perhaps the only definite indication of revascularization.[35] To conclude, management of patients with ARAS varies from person to person.

Stent Insertion

Stent insertion has the same success rate as of surgery (98% to 100%), but its morbidity and mortality is significantly less (3% to 6% severe complications and 10% to 20% minor complications).[132,133] Restenosis of stent occurs in 13% of patients within 6 to 24 months,[134] and then it will

Table 2. Indications of Renal Artery Revascularization

Clinical Indications	Radiographic Indications
Refractory hypertension	Stenosis of more than 75%
Refractory heart failure	Recent renal artery occlusion with normal kidney size
Acute kidney failure after using ACEIs	
Progression of kidney failure despite good control of hypertension	
Recurrent pulmonary edema associated with bilateral renal artery stenosis	
Severe renal artery stenosis in dialysis patients who started dialysis recently	

be removed with repeated angioplasty. Angioplasty without stent is not recommended and it can only slightly reduce blood pressure.[127,135,136] Angioplasty and stenting are not so effective in patients with severe ARAS, especially when ostium of the artery is involved. The success rate in this situation is only 50%, and the incidence of restenosis is 5% to 38%. In the majority of patients who undergo stenting, kidney failure continues to progress.

Some studies have shown that kidney function may remain stable or even improved after revascularization.[132,137-144] Improvement of left ventricular hypertrophy has also been demonstrated.[145] On the other hand, there are studies showing no benefit from revascularization neither on hypertension nor on kidney function.[138,146]

In one study, angioplasty plus stenting reduced cardiovascular mortality in those who had a GFR greater than 40 mL/min.[55] This result was also confirmed in patients in whom the entire mass of the kidney was affected by ARAS.[147] However, again most patients who underwent angioplasty or stenting showed no changes in GFR. The randomized trial of angioplasty only without stenting showed no beneficial effect for revascularization.[127] Two other studies using stenting also did not show any change in serum creatinine level.[137,148]

A comprehensive review comparing angioplasty alone with stenting, published in 2000, showed that stenting is superior to angioplasty and 65% to 70% of patients with stent did show stability or improvement of kidney function.[149] These retrospective studies have many biases and cannot be the basis for making decision for management of ARAS. To date, 6 randomized controlled trials comparing revascularization and medical treatment have been published (Table 3). All except one[150] had small sample sizes and short follow-up periods. The study of van de Ven and colleagues[146] compared angioplasty with stenting, but the studies of Van Jaarsveld and colleagues,[127] Webster and coworkers,[136] and Plouin and colleagues[135] compared angioplasty versus medical treatment. One of the trials[151] compared stenting with medical treatment. All of them showed no benefit in terms of kidney function improvement, but modest effect on blood pressure. All these studies were underpowered too in relation of primary endpoints including main cardiovascular events and kidney function outcomes. The Angioplasty and Stent for Renal Artery Lesions trial, the largest study to date, included 806 patients which were randomized to endovascular revascularization or standard medical treatment with good follow up period. Key findings in this trial were minor deterioration in kidney function over time in both groups, but no difference between them. In regard to blood pressure, renal events, vascular events, and mortality the two groups were comparable.

An ongoing multicenter trial[152] comparing the effect of optimal medical treatment plus stenting with medical treatment has not been published yet and it may address some of the controversies in the diagnosis and therapy of ARAS.

Although revascularization of patients with less than 70% stenosis is associated with no benefit,[127,135,137,139,140,146,148,153-155] no conclusion can be made based on these studies with regard to significant stenosis (> 70%). The study of Tuttle and colleagues showed that a wide range of patients with stenosis may benefit from stenting.[141] Diabetics and patients with nephrosclerosis are among them. The greatest benefit was seen in patients with kidney failure and congestive heart failure. Women with hypertension but nearly normal kidney function had better response in terms of controlling blood pressure. The problem is the group of patients who lose their kidney function during revascularization (19% to 25% of patients).[25,156] More than 35% of these patients may reach dialysis. It is obvious that the mortality rate among this group is high.[157] A study by Korsakas and coworkers showed that in 17.9% of patients, kidney function was deteriorated and 10.7% of patients died consequently.[158] The cause of this outcome is unknown, but undoubtedly, atheroembolies from injured atherosclerotic plaques play a role. The other possibility is the reperfusion injury process in association with activation of oxidative stress phenomenon.

Guidelines for Revascularization Based on Radiologic Findings

Patients with a kidney size of less than 8 cm or those with a resistive index greater than 0.80 are most unlikely good candidate for revascularization. The other factor is flow-volume relation, which can be measured by MRA. It means that if the volume of the kidney is preserved while the flow is reduced, revascularization may have some benefits.[159] This theory should be tested by further investigations.

Table 3. Data Characteristics of 6 Randomised Controlled Trials Comparing Angioplasty, Stenting, and Medical Therapy for Atherosclerotic Renal Artery Stenosis

Study	Patient Characteristics	Interventions	Number of Patients	Follow-up, mo	Outcome		
					Blood Pressure	Kidney Function	Others
van Jaarsveld et al[127]	ARAS + HTN Stenosis ≥ 60% serum creatinine ≤ 2.3 mg/dL	Angioplasty Medical therapy	106	12	Little advantage	No difference	Lower stenosis rates after 12 months with angioplasty
Plouin et al[135]	ARAS + HTN Stenosis ≥ 75% or ≥ 60% and positive lateralization test GFR ≥ 50 mL/min	Angioplasty Medical therapy	49	6	No benefit	No difference	Complication 3 times higher in the angioplasty group
Webster et al[136]	ARAS + HTN Stenosis ≥ 50% Serum creatinine ≤ 500 mmol/L	Angioplasty Medical therapy	55	3 to 45	Modest improvement in systolic blood pressure with angioplasty, particularly in bilateral ARAS, but no cure	No improve in kidney function by angioplasty	Significant complications in angioplasty group, but comparable event-free survival rates
van de Ven et al[146]	ARAS + HTN Stenosis ≥ 50% Positive captopril renography or ≥ 20% increase in serum creatinine after ACEI	Angioplasty Stenting	85	6	No difference	No difference	Patency rate better with stenting
Bax et al[151]	ARAS Stenosis ≥ 50% GFR < 80 mL/min	Stenting Medical therapy	140	24	…	No clear effect on progression of impaired kidney function	Small number of significant procedure-related complications
The ASTRAL Investigators[150]	ARAS Stenosis ≥ 50% (except in 6 patients with stenosis < 50%)	Stenting Stenting + medical treatment	806	60	No evidence of a worthwhile clinical benefit from revascularization	No evidence of a worthwhile clinical benefit from revascularization	Revascularization carried substantial risk

*ARAS indicates atherosclerotic renal artery stenosis; HTN, hypertension; GFR, glomerular infiltration rate; and ASTRAL, Angioplasty and Stent for Renal Artery Lesions trial.

Surgery

Nowadays, with the advent of invasive nonsurgical procedures, there is no place for surgery. The morbidity and mortality of surgery is high (20% to 40% and 5% to 8%, respectively).[155,156,160] However, in patients with aorto-iliac diseases, it is superior to interventional revascularization. It is also the choice in severe ostial stenosis and in patients in whom thrombosis has obstructed the renal artery. There are also some factors that determine which patients will benefit from the surgery. Kidney size of more than 8 cm, filling the artery distal to stenosis through the collaterals, good tracer uptake in scintigraphy, and normal tubules plus little glomerular sclerosis on pathologic examination are some factors that predict the outcome of surgery.

FUTURE DIRECTIONS

Based on clinical and paraclinical facilities and with a better risk profile, the prognosis of ARAS may improve in the future by achieving direct treatment of the disease, including finding the new medications and implementing better interventional techniques. For this purpose, the following questions should be addressed in well-designed studies in future: what is the best method for screening and diagnosis of ARAS? What is the exact prevalence of the disease in different subgroups (eg, patients with congestive heart failure, coronary artery disease, proteinuria, etc)? What is the natural course of ARAS and IN? What percentage of stenosis is functionally critical? Which biomarkers can show the early tissue damages? What is the effect of statins or ACE inhibitors or angiotensin receptor blockers on the natural course of ARAS? Who benefits from revascularization? What is the effect of revascularization on patient survival? What is the proper way to follow up patients with ARAS?

CONFLICT OF INTEREST

None declared.

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