Case Report

Two Cases of Renovascular Hypertension and Ischemic Renal Dysfunction: Reliable Choice of Examinations and Treatments

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We experienced two aged patients with atherosclerotic renovascular stenosis associated with hypertension and ischemic nephropathy. Both patients exhibited sudden rise in blood pressure (BP) and progressive aggravation of renal dysfunction. In these patients, the use of contrast medium to screen for renal artery stenosis (RAS) ran the risk of further deterioration of renal function. We therefore used magnetic resonance angiography (MRA), which is less conducive to renal damage, to screen for RAS. One-sided RAS was treated by percutaneous transluminal angioplasty of the renal artery (PTRA) and stenting. As a result, BP decreased in both patients. Serum creatinine (Cr) decreased slightly in one patient, whereas, in the other, serum Cr increased transiently and then decreased and stabilized to pre-treatment levels. Thus, although it is unclear whether the combination of PTRA and stenting is among the best treatments for patients with RAS and moderate-to-severe renal dysfunction, PTRA and stenting are clearly of benefit in selected patients. In addition, recent progress in characterizing the pathophysiology of ischemic nephropathy associated with renovascular hypertension has created interest in the therapeutic potential of angiotensin II receptor antagonists, sympatholytic agents, and antioxidants. Therefore, we discuss the therapeutic utility of PTRA and stenting and the above-mentioned medications in patients with RAS and renal dysfunction.

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Key Words: magnetic resonance angiography, percutaneous transluminal angioplasty of the renal artery, renin-angiotensin system, sympathetic nervous system, oxidative stress

Introduction

Ischemic nephropathy, which is defined as renal dysfunction due to renal hypoperfusion mainly through renal artery stenosis (RAS), is one of the major causes of chronic renal failure (1, 2). Moreover, its prevalence is underestimated because renal angiography using a contrast medium is not usually performed due to the potential risk of further deterioration of renal function, especially in patients with abnormal renal function. In addition, ischemic nephropathy often coexists in patients with hypertensive renal disease. This concept

is compatible with the fact that cardiovascular diseases are often associated with end-stage renal disease (3). In a report by Uzu *et al.* (4), RAS was found in approximately half of patients with renal dysfunction and atherosclerotic disease. Peripheral vascular disease and carotid atherosclerosis were particularly frequent in patients with RAS (4, 5). Moreover, the survival rate was low in patients with renal dysfunction and RAS (4). The poor prognosis of patients with abnormal renal function due to RAS may be related to concomitant cardiovascular diseases and especially to an accelerated progression of renal failure: in half of patients with atherosclerotic disease of the renal artery, RAS progresses gradually,

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Fig. 1. Renal magnetic resonance angiographic findings in case 1. Severe (right) and moderate (left) stenosis was observed in the renal artery (arrows).

and 1/10 to 1/8 of these patients fall into complete obstruction of the renal artery (2).

In addition, the prevalence of RAS has been reported to be especially high in elderly subjects, even in the absence of apparent renal dysfunction (6, 7). In an ageing society such as that of modern Japan, early diagnosis and treatment of RAS is important. Recent advances in strategies to diagnose and treat renovascular hypertension will be helpful to prevent the development of renal dysfunction in patients with ischemic nephropathy. In this report, we describe our choice of examinations and treatments in two aged patients with renovascular hypertension associated with ischemic nephropathy, and discuss the pathophysiology of RAS and ischemic nephropathy in relation to these cases.

Case Report

Case 1

A 74-year-old man was admitted to our hospital for examination and treatment of progressive renal dysfunction associated with hypertension in March 2004. His serum creatinine (Cr) level was already high (1.7–1.9 mg/dl) in March 2003, although it was approximately 1.0 mg/dl prior to then. His blood pressure (BP) was 125–135/75 mmHg at that time. In October 2003, his BP was suddenly elevated to 170/110 mmHg. Although the BP level was controlled within 130–150/70–90 mmHg using amlodipine (2.5 mg/day) and candesartan (4 mg/day), the renal function progressively deteriorated (blood urea nitrogen [BUN], 33 mg/dl; serum Cr, 2.3 mg/dl). After that, amlodipine was discontinued because BP was controlled well with candesartan alone. However, candesartan was changed to doxazosin (2–4 mg/day), because serum Cr was slightly but further elevated (2.6–2.8 mg/dl). Because plasma renin activity (PRA) was high (8.9 mg/ml/h), renal magnetic resonance angiography (MRA) was per-

formed to screen for renovascular hypertension in February 2004. Stenosis was observed at the ostia of the bilateral renal arteries (Fig. 1), and the right RAS was more severe than the left RAS. The patient was admitted to our hospital for further examination and treatment with a tentative diagnosis of renovascular hypertension.

Physical examination on admission showed high normal BP (138/78 mmHg), bruit on the right carotid area and optic bulb, and pretibial edema. However, abdominal bruit was not heard. BUN and serum Cr were 34.3 and 2.1 mg/dl, respectively. The Cr clearance was 34.5 ml/min. PRA was not increased (1.4 mg/dl/h), but plasma aldosterone concentration (PAC) was elevated slightly (15.5 ng/dl). Urinalysis did not reveal any abnormal findings. He had slightly small kidneys, as measured by ultrasonography (right: 9.6 × 4.1 cm; left: 8.7 × 4.8 cm). Captopril-stimulated ¹³¹I-ortho-iodohippurate renography showed the delayed peak uptake and excretion of isotope in the right kidney. On the other hand, in the left kidney, the curve was not delayed although the peak of the renogram was extremely low. We confirmed the bilateral RAS with aortography. In addition, renal venous PRA was 2.6 and 1.5 ng/ml/h in the right and left kidneys, respectively.

Therefore, percutaneous transluminal angioplasty of the renal artery (PTRA) and stenting were performed in the right kidney. PRA in the right renal vein was increased to 6.1 mg/ml/h just after PTRA. Although the case was complicated by bleeding of the puncture region, the antihypertensive agent could be discontinued. Serum Cr was transiently elevated to 2.66 mg/dl just after PTRA, but then decreased to approximately 2.4 mg/dl and was stable thereafter.

Case 2

A 70-year-old woman was admitted to our hospital for severe hypertension and increase in serum Cr in September 2000. She had been diagnosed with hypertension in 1974. Her BP was suboptimally controlled in spite of her using multiple antihypertensive drugs at that time. In 1980, she was admitted to a hospital for myocardial infarction. In 1994, she visited a clinic for extremely high BP (180–190/110 mmHg) and was referred to our hospital because of hypokalemia, low PRA, and high PAC. Adrenal scintigraphy and adrenal venous sampling revealed primary aldosteronism in right adrenal adenoma. Therefore, a right adrenalectomy was performed. After the adrenalectomy, her BP could be controlled to around 130/90 mmHg with diltiazem (100 mg/day) and doxazosin (1 mg/day). In 2000, however, the BP level was again suddenly elevated to 190/110 mmHg, sometimes in association with headache. Addition of atenolol (25 mg/day) was not effective. Also, serum Cr was increased slightly at the same time.

On admission, her BP level was 193/89 mmHg and abdominal bruit was heard. BUN was 31 mg/dl and serum Cr was 1.61 mg/dl. PRA was 1.0 mg/ml/h and PAC was 2.7

Fig. 2. Renal magnetic resonance angiographic findings in case 2. Severe stenosis was observed in the bilateral renal arteries (arrows).

ng/dl. Bilateral kidneys were not atrophied (right: 10 cm in length; left: 9 cm; as measured by ultrasonography). Renal MRA showed severe stenosis at the ostia of the bilateral renal arteries (Fig. 2). Bilateral RAS was confirmed by aortography. PRA in the right and left renal vein were 11.3 and 3.6 ng/ml/h, respectively.

In the right renal artery, PTRAs and stenting were done. After that, PRA in the right renal vein decreased to 4.2 ng/ml/h. BP was reduced to 150/90 mmHg, and serum Cr decreased to 1.0–1.2 mg/dl and was stable thereafter.

Discussion

Diagnosis of RAS

Renovascular hypertension has been associated with several clinical features, such as relatively old age (6, 7), sudden elevation of BP, and accelerated progression of renal dysfunction; all of these features were seen in both of the present cases. Possible deterioration of renal function induced by inhibition of the renin-angiotensin (R-A) system, as in case 1, also suggests renovascular hypertension. Moreover, as in case 2, severe and uncontrollable high BP is compatible with RAS-induced hypertension: Its prevalence is less than 1% among all patients with hypertension but is approximately 20% in patients with malignant hypertension (1). Abdominal bruit (case 2) is one of the characteristic physical findings for RAS, although vascular bruit in other regions (case 1), which often indicates atherosclerotic changes, is also compatible with renovascular disease (3). We therefore specifically examined for renovascular hypertension in both of the present cases.

Aortography and renal angiography are standard procedures for the precise diagnosis of RAS. Concomitantly, PRA can be measured in a blood sample from the renal vein, and used to determine whether RAS activates renal renin production. However, because the contrast media used in these in-

vasive procedures run the risk of further deteriorating renal dysfunction, the procedures should only be adopted to assess the need for invasive intervention in patients with highly-speculative renovascular disease. To simply screen for RAS, less invasive procedures should be suitable. For example, in digital subtraction angiography (DSA), a smaller amount of contrast medium is used. CT angiography and helical CT also require small amounts of contrast medium. However, these procedures still may not be suitable for patients with renal failure due to the nephrotoxicity of a substantial amount of contrast medium. On the other hand, renal Doppler ultrasonography is a non-invasive procedure and useful even in patients with renal failure. However, the accuracy of the procedure is dependent on who performs it. Moreover, the Doppler wave is sometimes not detected, especially in patients with obesity or a lot of intraabdominal gas. Renography is also non-invasive and useful for diagnosis not only of unilateral RAS but also of remnant renal function of the stenotic kidney, but its specificity and sensitivity are low in patients with renal failure. Although the use of a captopril (8) strengthens the usefulness of renography, as in case 1, the limitations of renography are not completely overcome by this modification. Another non-invasive method is MRA (9), which is also useful even in renal failure. And its accuracy does not depend on the skillfulness of the individual technician. Actually, in the two present patients, both of whom showed renal dysfunction, MRA was useful for screening RAS: MRA is one of the most useful strategies for screening RAS in aged patients with ischemic nephropathy and atherosclerosis.

Although activation of the R-A system is the primary cause of high BP and renal damage in renovascular hypertension, PRA is sometimes not increased, either because of a volume expansion due to renal dysfunction or because of the action of some antihypertensives (treatment with multiple antihypertensive agents is often required to control BP). Indeed, in both of the present patients, PRA was not particularly high. Rather than PRA in peripheral blood, PRA in the renal vein may reflect the intrarenal R-A system accurately, although renal venous sampling is an invasive examination. In the present patients, the PRA data of venous sampling was used to confirm the activation of the R-A system at the time of PTRAs and stenting. In case 1, the PRA was 1.73 times higher in the right renal vein than the left vein, which was compatible with the finding of MRA and aortography. The PRA was 3.14 times higher in the right renal vein than the left vein in case 2, although the imaging of the renal arteries could not differentiate the pathophysiological status between the right and left kidneys. We performed PTRAs and stenting in the renal artery of the kidney that was larger and that had the higher venous PRA. Our decisions were proven correct, since revascularization of the renal artery resulted in BP reduction and amelioration (or preservation) of renal function in both patients.

Revascularization of the Renal Artery

Revascularization of the renal artery is a somewhat radical treatment for renovascular hypertension. PTRAs, on the other hand, is a less invasive and more popular procedure than surgical revascularization (*1*). However, there are several limitations to PTRAs, such as the risks of technical failure, vascular accident (dissemination or rupture, and occlusion of the side-branch artery), renal infarction, bleeding and/or hematoma, and infection. Contrast nephrotoxicity might occur within 2 to 5 days after PTRAs. Also, microembolization into the kidney might increase serum Cr levels. Even after successful revascularization, restenosis may occur, especially in patients with atherosclerotic renovascular hypertension. Stenting with PTRAs may prevent restenosis: it is more beneficial in ostial RAS-induced hypertension and nephropathy, while it is not conclusive whether the stenting is beneficial in all types of RAS (*1*).

The aim of renal artery revascularization is to lower BP as well as to protect renal function. The antihypertensive effect of revascularization has been established, but complete normalization of BP is sometimes not achieved, possibly due to hypertension-induced vascular damage. The administration of antihypertensive agents can overcome this limitation. There is not consistent evidence of the renoprotective effect of revascularization of the renal artery in renovascular hypertensive patients with more than 1.5–2.0 mg/dl of serum Cr. This is critical, because the amelioration and stabilization of renal function are often difficult to achieve by medication. In patients with relatively small kidneys (length, <8 cm), it has been suggested that revascularization has no beneficial effect on renal function (*3*). BP levels do not influence the prognosis of renal function after revascularization. In our two patients with bilateral RAS, we performed PTRAs with stenting in the larger of the two kidneys, since it was expected that there was a better chance of restoring renal function in the larger kidney. As a result, renal function was slightly ameliorated in case 2. On the other hand, serum Cr was transiently increased in case 1, which may have been due to microembolization in the right kidney: PRA in the right renal vein was elevated just after PTRAs. However, PRA decreased to the baseline level and stabilized thereafter. Thus, some other possibility, such as the influence of contrast medium, might also be considered. Although, in our patients, PTRAs with stenting exhibited some beneficial effects, the RAS-induced ischemic nephropathy may be treated by medication in addition to revascularization of renal artery.

The Intrarenal R-A System in Renovascular Hypertension

Renovascular hypertension is considered to be caused by activation of the R-A system through renal ischemia with RAS: the long, negative-feedback loop of the R-A system is broken *via* renal hypoperfusion in spite of elevated BP. In cases

of bilateral RAS, such as those of the two present patients, sodium retention due to renal dysfunction suppresses the systemic R-A system, with the result that the R-A system is apparently normalized. Similarly, the systemic R-A system is not always activated in the chronic phase of renovascular hypertension associated with renal failure. However, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (AII) receptor antagonists have beneficial effects in more than 80% of patients with renovascular hypertension (*10*). Therefore, the intrarenal R-A system may be enhanced in patients with RAS-induced hypertension although the systemic R-A system is not.

In the acute phase (7 days after clipping) in 2-kidney, 1-clip (2K1C) rats, the AII content in both stenotic and non-stenotic kidneys has been shown to be elevated in association with increased plasma AII (*11*). In chronic phase (25 days after clipping), both intrarenal AII contents were still elevated, although plasma AII had already returned to normal levels. Moreover, in the other animal models with elevated AII, such as AII-infused rats and Ren2 transgenic rats, intrarenal AII content was increased more prominently than plasma AII. Thus, it is suggested that enhancement of plasma AII increases intrarenal AII content. Recent reports have suggested a mechanism by which this effect may occur. First, the kidney has been demonstrated to uptake exogenously-administered AII (*12*), and secondly, chronic AII infusion was shown to cause upregulation of renal angiotensinogen mRNA and protein levels in rats (*13*). AII receptor antagonists normalized these effects of AII infusion. Therefore, AII type 1 receptor may mediate AII uptake and AII overproduction in the kidney, which may increase intrarenal AII content in renovascular hypertension, leading to progression of hypertension and renal damage even without stimulation of the systemic R-A system (Fig. 3). Alternatively, agents that inhibit the R-A system may have beneficial effects on the prognosis of renovascular hypertension either with or without an increase in PRA. Moreover, AII receptor antagonists may more completely ameliorate BP rise and impairment of renal function compared with ACE inhibitors. This concept is compatible with earlier experimental results in dogs with RAS: ACE inhibitor did not completely suppress progression of hypertension and renal dysfunction (*14*). However, it does not exclude the possibility that factors other than activation of the intrarenal R-A system may also play a role in the pathophysiology of renovascular hypertension.

Sympathetic Overactivation in Renovascular Hypertension

In patients with renovascular hypertension, sympathetic nerve activity has been reported to be enhanced based on measurement of muscle sympathetic nerve activity (*15, 16*) and plasma norepinephrine concentration (*15*). In rats, renal denervation prevented RAS-induced hypertension (*17*).

Fig. 3. Angiotensin II (AII) excess stimulates the intrarenal renin-angiotensin system. Intrarenal AII is derived from uptake of extrarenal AII and intrarenal production, both of which occur through AII type 1 receptor. Thus, AII receptor antagonist may more completely block increase in intrarenal AII content compared with angiotensin-converting enzyme (ACE) inhibitor because ACE inhibitor can inhibit only partially intrarenal AII production.

Moreover, sympathetic excitatory responses to environmental stressors were enhanced in 2K1C rabbits: an air-jet stress elicited a marked increase in renal sympathetic activity and mean BP, which was inhibited by rilmenidine, an α adrenoreceptor agonist (18). Thus, the sympathetic nervous system may play a role in the pathophysiology of renovascular hypertension. Increased sympathetic nerve activity has been observed in several renal diseases as well as renovascular hypertension. In addition, renal ischemia is probably a primary event leading to sympathetic activation (19). Restoration of renal perfusion in humans with renovascular hypertension reduces muscle sympathetic nerve activity to control levels, in association with the normalization of BP (16). Sympathetic activation has been observed in hypertensive subjects with polycystic kidney diseases and normal renal function (20), and thus it is conceivable that renal cysts cause the localized intrarenal ischemia. Also, rats with phenol-induced renal injury have been reported to exhibit hypertension associated with increased renal sympathetic nerve activity and norepinephrine secretion from the posterior hypothalamic nuclei (21). Losartan ameliorated hypertension in association with a reduction in the central and peripheral sympathetic nerve overactivity. Also, enalapril decreased muscle sympathetic nerve activity, ameliorated abnormal baroreflex curve, and reduced BP in patients with chronic renal failure (22). Thus, activation of the R-A system may at least partly contribute to the sympathetic nerve stimulation, although it is not the sole cause of the sympathetic nerve overactivity. In support of this hypothesis, bilateral dorsal rhizotomy suppressed the development of hypertension in rats with 5/6 nephrectomy in association with a reduction of norepinephrine turnover in the posterior and lateral hypothal-

Fig. 4. Stimulated sympathetic nervous system in ischemic nephropathy. In renal artery stenosis (RAS)-induced ischemic nephropathy, in addition to sympathetic activation by activation of the renin-angiotensin (R-A) system, ischemia itself increases the sympathetic nerve activity through chemoreceptor stimulation.

amic nuclei and locus ceruleus (23). Thus, afferent stimuli from a diseased kidney may contribute to the sympathetic activation in renal failure (Fig. 4).

More importantly, the sympathetic nervous system may contribute to the progression of renal disease. Although adrenergic nerve fibers do not penetrate the glomerulus (24), podocytes have adrenoreceptors and purinoreceptors (25, 26). Thus, a direct effect of the sympathetic nervous system may lead to podocyte constriction and proteinuria, independent of their hemodynamic change. In fact, in a study using a subtotal nephrectomy model, Amann *et al.* (27) reported that adrenergic blockade conferred podocyte protection without a change in BP. Several investigators have demonstrated that β -adrenergic receptor blockade resulted in renal protection in several models of renal dysfunction, such as 5/6 nephrectomy, nitric oxide (NO) inhibition, and salt-loaded stroke-prone spontaneously hypertensive rats (27–30). Third generation β -blockers, such as carvedilol and nebivolol, seem to have more protective effects than traditional β -blockers, possibly *via* stimulation of NO. Renal protection by α -adrenergic blockade has also been observed in several renal failure animals (27, 30). A combination of α - and β -adrenergic blockade has been shown to be more effective in reducing renal damage in a subtotal nephrectomy model than α blockade alone (27). A similar beneficial effect was observed in this model with the central sympatholytic agent moxonidine (31) and renal denervation (32). Recently, moxonidine superimposed on some agents to inhibit the R-A system delayed loss of renal function in patients with advanced renal failure, whereas superimposing nitrendipine did not (33). Al-

Table 1. Role of Reactive Oxygen Species (ROS) Overproduction in Renal Damage by Renal Artery Stenosis (RAS)

	Atherosclerotic RAS	Other cause of RAS
ROS production		
Cortical perfusion		
Medullary perfusion	*	~
Medullary HIF-1 α levels		
Renal damage	**	~

* Possibly due to medullary vasoconstriction by excess of ROS.

** Renal medulla is liable to be more damaged by hypoxia compared with renal cortex. , increase; , decrease; ~, unchange.

Fig. 5. Protective role of hypoxia-inducible factor-1 α (HIF-1 α) for hypooxygenemia in renal medulla. In the renal medulla, HIF-1 α , induced by medullary hypooxygenemia, contributes to the adaptation to low P_{O_2} through transcription of oxygen-sensitive genes. However, ROS downregulates the HIF-1 α level, which impairs the adaptive response of many cells to oxygen-sensitive genes, resulting in disturbance of renal medullary adaptation to low P_{O_2} .

though there have been few studies on this subject with the exception of the reports mentioned above, the sympatholytic agents may be among the possible medications for treating renovascular hypertension in conjunction with a blockade of the R-A system.

Role of Oxidative Stress in Renovascular Hypertension

RAS itself induces overproduction of reactive oxygen species (ROS): Higashi *et al.* (34) demonstrated that patients with renovascular hypertension exhibited impairment of endothelial function in association with ROS overproduction, which was ameliorated by renal angioplasty. This finding is reasonable because the R-A system is well known to stimulate ROS generation. Because antioxidants such as vitamin C (34) ameliorated endothelial dysfunction in patients with renovascular hypertension, ROS may accelerate damage of the kidneys and other tissues. Clinical studies have consis-

tently demonstrated that atherosclerotic RAS has more unfavorable outcomes than other causes of RAS, suggesting that additional mechanisms may contribute to the deleterious effect of hypoperfusion on the kidney and augment renal injury. In a recent report (35), rats fed a hypercholesterolemic diet showed an increase in the RAS-induced production of serum Cr, suggesting that RAS-induced renal damage may be enhanced by early atherosclerosis. Generally, RAS itself impairs the cortical hemodynamics of the kidney, but leaves the renal medulla relatively preserved (36); however, hypercholesterolemic diet in addition to RAS has been shown to reduce medullary as well as cortical perfusion (35) (Table 1). In the latter study, basal cortical perfusion and single-kidney glomerular filtration rate were decreased similarly in the RAS and the RAS-plus-hypercholesterolemia groups, whereas tubular fluid reabsorption was markedly impaired only in the RAS-plus-hypercholesterolemia group. Moreover, ROS production was enhanced more greatly in the RAS-plus-hypercholesterolemia group than in the group receiving RAS alone. Early atherosclerosis facilitates vascular ROS generation, which causes a vasoconstrictive response (37, 38); thus, ROS-induced vasoconstriction may disturb the mechanism for regulating renal medullary hemodynamics, resulting in accelerated hypoperfusion of the renal medulla.

However, hypoperfusion itself might not be critical for the renal medulla, which is primarily underperfused: the poor medullary blood perfusion results in a low P_{O_2} milieu (about 20 mmHg in the outer medulla and 10 mmHg in the papilla) (39, 40). Thus, the renal medulla is considered to have a mechanism for adapting to low P_{O_2} . Recently, Zou *et al.* (39) proposed that hypoxia-inducible factor-1 (HIF-1) plays an important role in hypoxia-induced molecular adaptation in the renal medulla. Indeed, HIF-1 α mRNA and protein are expressed at high levels in the renal inner medulla (41). In the renal medulla, HIF-1 α , induced by medullary hypooxygenemia, contributes to the adaptation to low P_{O_2} through transcription of oxygen-sensitive genes, such as those encoding erythropoietin, vascular endothelial growth factor, inducible NO synthase, heme oxygenase-1, and transferrin. However, ROS downregulates the HIF-1 α level, and this change impairs the adaptive response of many oxygen-sensitive genes to cell hypoxia: in cultured renal medullary interstitial cells, hypoxia-induced HIF-1 α levels were abolished by superoxide and, conversely, superoxide dismutase and its mimetic Tempol increased HIF-1 α expression (42). Thus, ROS may disturb renal medullary adaptation to low P_{O_2} , and this phenomenon may occur through inhibition of hypoxia-induced production of HIF-1 α in addition to its hemodynamic changes (Fig. 5, Table 1). Indeed, because antioxidant vitamins have been shown to ameliorate renal injury in RAS model animals (43), antioxidant therapy may be an additional choice to prevent RAS-induced renal damage, especially in patients with atherosclerotic renovascular hypertension.

In conclusion, we reported the cases of two aged patients with bilateral renovascular hypertension and ischemic

nephropathy. In these cases, MRA was especially useful as a screening method. And PTRAs with stenting at least stabilized renal function, which had been progressively deteriorated. Although several risks exist in this therapeutic procedure, in some cases with ischemic nephropathy it is worthwhile to perform the procedure under careful evaluation of renal function. Moreover, there are several choices of possible therapies for renovascular hypertension, *i.e.*, AII receptor antagonists, sympatholytic agents, and antioxidants.

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