

## Refractory hypertension after renal transplantation

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■ Hypertension is a common problem encountered after renal transplantation. Many different mechanisms may be responsible for hypertension in this setting, and therapy will depend upon the mechanism(s) affecting the individual patient. Factors that may cause or aggravate post-transplantation hypertension include renal dysfunction secondary to rejection or other diseases of the transplanted kidney, renin production from the diseased native kidneys if these kidneys have not been surgically removed, extracellular fluid volume expansion, toxic effects of medications used after transplantation, especially cyclosporine and intravenous prednisolone, or primary hypertension in the donor or recipient. Renal artery stenosis may predispose to acute renal failure in the presence of treatment with angiotensin-converting enzyme inhibitors. Severe renal artery stenosis may also lead to refractory salt and water retention and fluid overload with congestive heart failure and hypertension, mediated primarily due to extracellular fluid volume excess. Therapy with percutaneous transluminal renal angioplasty or, as a last resort, surgery, can be successful in controlling these problems.

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A 24-YEAR-OLD white woman presented to the Cleveland Clinic in 1987 with end-stage renal disease. Her brother also had chronic renal failure, but was not yet receiving dialysis treatment. No other family members had renal disease. After an evaluation that included renal ultrasound, medullary cystic disease was diagnosed. Hemodialysis was begun, and the patient was maintained on this therapy for six months. She then received a cadaveric renal transplant. While she was receiving dialysis treatment,

her blood pressure ranged between 130-150/70-90 mmHg without antihypertensive medication.

After transplantation, she experienced acute renal failure, and she was treated with antilymphocyte globulin, azathioprine, and prednisone. The acute renal failure was non-oliguric, and she required only one postoperative dialysis procedure. On the sixth postoperative day, her creatinine level decreased spontaneously, and by the 15th postoperative day, her creatinine level was 1.9 mg/dL. Antilymphocyte globulin was discontinued, and cyclosporine therapy was initiated; prednisone and azathioprine were also maintained.

Three weeks after transplantation, the patient was admitted to the hospital with an episode of rejection. Her serum creatinine level had increased from 1.8 mg/dL to 4.5 mg/dL. She was treated with intravenous methylprednisolone (500 mg/d for 3 days), followed by

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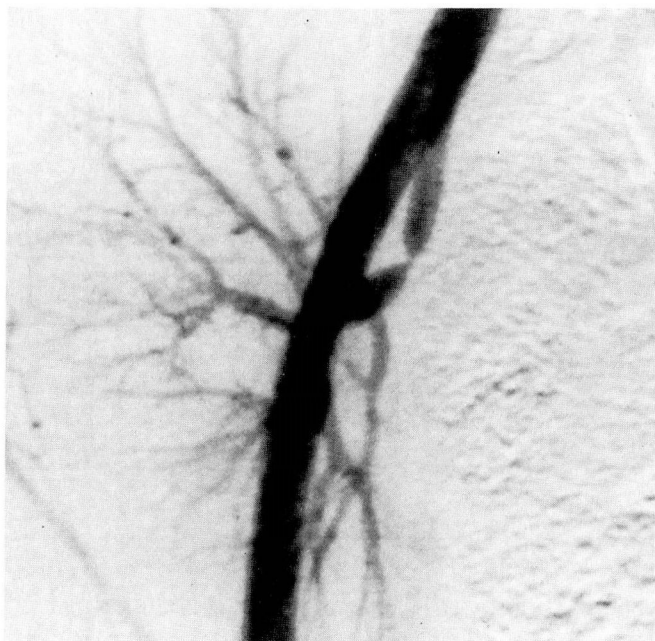


FIGURE 1. Renal arteriogram demonstrating severe stenosis in the renal artery in a 24-year-old woman, four months post-renal transplantation.

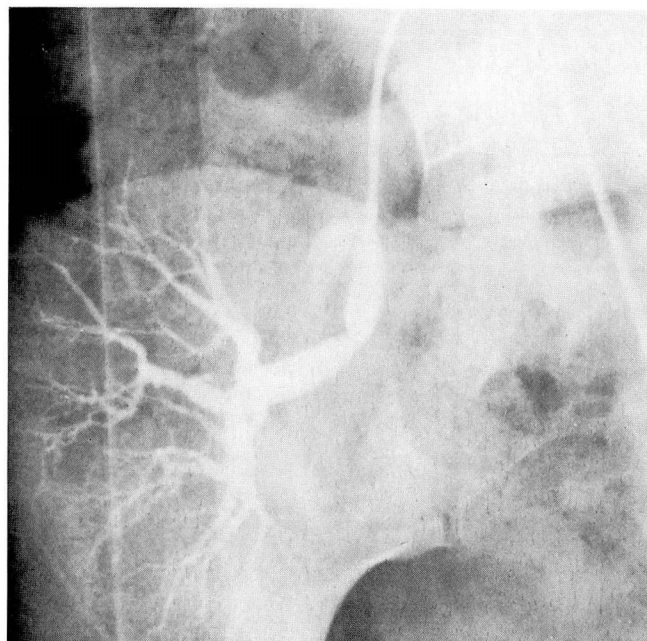


FIGURE 2. Percutaneous transluminal renal angioplasty with successful dilatation of the renal artery in the same patient.

two additional doses on alternate days for a total of 2.5 g. Her serum creatinine level decreased to 2 mg/dL.

Immediately after transplantation the patient's blood pressure was normal without antihypertensive medications. However, eight weeks after transplantation, hypertension developed, which was somewhat difficult to control in part because she did not tolerate antihypertensive medications very well. She was treated with varying regimens, including the following medications: nifedipine, verapamil, labetalol, hydralazine, clonidine, and hydrochlorothiazide.

Three months after transplantation, the patient was admitted to the hospital again when her serum creatinine level increased from 2.4 mg/dL to 4.8 mg/dL. An acute rejection episode was diagnosed. She was treated with muromonab-CD3 (Orthoclone OKT3), and her serum creatinine level declined to 3.9 mg/dL.

Four months after transplantation, the patient was readmitted to the hospital because oligo-anuria suddenly developed, and her creatinine level increased from 3.9 mg/dL to 6.2 mg/dL over a 24-hour period. This episode occurred immediately after she received a 5-mg dose of lisinopril. The patient remained oliguric for five days and required one hemodialysis procedure despite discontinuation of the lisinopril after the one initial dose. After hemodialysis, her urine output increased,

and the acute renal failure gradually resolved. A renal arteriogram was obtained, and severe stenosis of the renal artery was identified (*Figure 1*). Percutaneous transluminal renal angioplasty (PTTRA) was performed, and the renal artery was successfully dilated (*Figure 2*). The patient's blood pressure improved after dilatation, and as of January 1989, her blood pressure was 140/80 mmHg while she was receiving verapamil sustained-release form (Calan SR), 240 mg daily. Her renal function remained stable, and her creatinine level was 1.7 mg/dL.

#### DISCUSSION

##### Etiology

Hypertension is often encountered after organ transplantation; approximately 80% of renal transplant recipients may become hypertensive.<sup>1-7</sup> A variety of mechanisms predispose to the development of hypertension in this clinical setting (*Table 1*). When managing transplant recipients with hypertension, the physician must direct the diagnostic and therapeutic interventions with these mechanisms in mind in order to optimize therapy for the individual patient.

Hypertension developed in the patient described above within the first few months after transplantation. During this time, she was receiving reasonably high



doses of cyclosporine and prednisone and had received intravenous methylprednisolone (Solu-Medrol) as treatment for rejection. Her hypertension was most likely due to the combined effects of the medications, superimposed on renal dysfunction that was associated with the rejection process. In addition, extracellular fluid volume expansion may have been a significant factor. She may have had some salt and water retention, although her clinical examination did not reveal significant edema or weight increases indicative of such a problem. However, some salt and water retention (<5%–10% of her extracellular fluid volume) may have escaped clinical detection.

### Effects of methylprednisolone and cyclosporine therapy on post-transplant hypertension

It is well recognized that intravenous methylprednisolone treatment for acute rejection episodes may be associated with acute aggravation of hypertension. Sometimes such exacerbation may progress to an accelerated phase and require aggressive parenteral treatment to control blood pressure. Usually, extracellular fluid volume expansion occurs because of the treatment superimposed on the rejection process, both of which will lead to salt and water retention. This patient, however, did not have any worsening of hypertension during her rejection episode and its treatment.

With the expanded use of cyclosporine for various types of organ transplants, in addition to autoimmune disorders, it has become clear that this agent will cause a syndrome very similar to primary hypertension, even in patients without any underlying hypertensive disorder.<sup>8–11</sup> Sometimes hypertension may become severe and even lead to an accelerated phase refractory to treatment. The most likely explanation for this patient's hypertension was such a cyclosporine-related effect that developed after her first rejection episode.

Cyclosporine produces significant effects on kidney function. In both humans and animals, after cyclosporine is administered, renal blood flow is reduced and the glomerular filtration rate is decreased.<sup>12–14</sup> These effects, which tend to be reversible even up to a year after therapy, are probably due to hemodynamic changes that occur possibly secondary to changes in prostaglandin metabolism that impair renal blood flow.<sup>15,16</sup> There also appears to be a separate effect of reducing the glomerular filtration rate, although much of the reduction in the glomerular filtration rate is due to increased renal resistance and decreased renal blood flow. Patients treated with cyclosporine have impaired salt and water excretion and probably a blunted pressure natriuresis re-

**TABLE 1**  
ETIOLOGIC FACTORS FOR POST-TRANSPLANT HYPERTENSION

Renal dysfunction secondary to rejection or other disease in the transplanted kidney <sup>1,3,5</sup>
Excess renin production from the diseased native kidneys if not surgically removed <sup>3,18–21</sup>
Expansion of extracellular fluid volume due to the failure of the transplanted kidney to normally excrete salt and water. This may be due to rejection, drugs, or other factors <sup>17</sup>
The hypertensive effect of medications, especially including cyclosporine, <sup>8–11</sup> intravenous Solu-Medrol, and ? prednisone <sup>30</sup>
Stenosis of the large arteries supplying blood to the transplanted kidney (aorta, iliac, or transplanted renal artery) <sup>28,31–34</sup>
Underlying primary hypertension in the donor and/or recipient <sup>35,36</sup>

sponse. Expanded extracellular fluid volume may also contribute to the hypertensive state.<sup>17</sup>

A significant improvement in blood pressure usually occurs when the dosage of cyclosporine is reduced. The high doses required immediately after transplantation (6–14 mg/kg/d) are more likely to aggravate the hypertension, whereas the doses used chronically in renal transplant recipients (2–6 mg/kg/d) do not seem to aggravate the hypertension.

### Renin-mediated hypertension and the use of ACE inhibitors

Renin-mediated hypertension was an issue in this woman's case because she retained her own diseased native kidneys after successful renal transplantation. Such patients have a higher incidence of hypertension than if the kidneys had been surgically removed.<sup>3,18–21</sup> This clinical setting is analogous to the experimental model of two-kidney, one-clip hypertension, which is predominantly renin-mediated.<sup>21</sup> Studies have indicated that treatment with an angiotensin-converting enzyme (ACE) inhibitor or surgical removal of the diseased native kidneys will lead to significant reductions in blood pressure as well as improvement in renal blood flow to the transplanted kidney.<sup>21</sup> Presumably, the excess renin and angiotensin result in increased vasoconstriction systemically and also in the renal vasculature.

This mechanism is probably the most important factor for patients who have a normally functioning transplanted kidney and who are not treated with cyclosporine. It may have played a role in this patient's case when her hypertension worsened despite relatively normal allograft function as assessed by serum creatinine measurements.

Another renin-related mechanism that can occur within a few months of transplantation is renal artery stenosis of the transplanted kidney. It is analogous to the

one-kidney, one-clip animal model of hypertension. In order to determine the most appropriate treatment for post-transplant hypertension, these mechanisms must be kept in mind.

#### Drug therapy for post-transplant hypertension

**Calcium channel blockers.** This patient received a calcium channel blocker, nifedipine (Procardia), early in her post-transplant course as initial treatment for hypertension. In general, calcium channel blockers are the most effective medications for cyclosporine-related hypertension.<sup>11</sup> Experimentally, they counteract some of the adverse renal effects of cyclosporine<sup>22</sup> by decreasing renovascular resistance, increasing renal blood flow, and raising the glomerular filtration rate. Thus, these agents may restore values to pre-cyclosporine treatment levels. Unfortunately, some patients, like this woman, do not tolerate nifedipine because of side effects such as palpitations, headache and flushing, and mild pedal edema. These effects are probably related to the drug's vasodilatory action.

However, nifedipine is still the most effective antihypertensive agent in the clinical treatment of hypertension associated with cyclosporine administration.

A long-acting nifedipine preparation currently undergoing clinical trials may lower the incidence of side effects. Administration of the drug with food also reduces the incidence of symptoms. Verapamil (Calan, Isoptin) and diltiazem (Cardizem) are also effective antihypertensive drugs, and sustained-release preparations (Calan SR, Isoptin SR, Cardizem SR) are more convenient for many patients. However, verapamil and diltiazem pose a risk for cyclosporine nephrotoxicity because they slow the metabolism and may increase the blood levels of cyclosporine. This effect may be beneficial by maintaining more therapeutic levels of cyclosporine and reducing the risk of rejection.

**Alpha- and beta-adrenergic blockers.** If calcium channel blockers are not tolerated or are not effective, then a variety of drugs can be employed on a trial-and-error basis for early post-transplant hypertension related to cyclosporine and/or rejection combined with variable degrees of extracellular fluid volume expansion. Beta- and alpha-blocking agents, centrally acting sympathetic blocking agents, and diuretics (usually loop diuretics if there is any degree of renal insufficiency leading to extracellular fluid volume expansion) are often useful in controlling hypertension. Direct-acting vasodilators may be added as more potent agents to help control blood pressure in the refractory case, although their propensity to cause salt and water retention may limit their

usefulness. This problem is especially true of minoxidil and limits its use.

Of some concern with beta blockers is their potential for decreasing renal blood flow, which may be associated with beta blockers that do not have significant cardioselectivity or alpha or intrinsic sympathomimetic activity (ISA). Also, potent vasodilators such as minoxidil may decrease renal blood flow and further impair renal function. Thus, beta blockers with ISA activity or combined beta and alpha blockers may be preferable to avoid renal vasoconstriction. Minoxidil should be used only as a last resort for the patient with very refractory hypertension.

**Stepped-care.** For difficult-to-control hypertension, a stepped-care approach should be employed, using increased dosages of drugs that combine different mechanisms of action. In some cases, patients may need to receive a beta blocker, calcium channel blocker (preferably a dihydropyridine to avoid conduction abnormalities that may be additive with the beta blocker), a centrally acting sympathetic blocker, an alpha blocker, and a diuretic. For acute control of hypertension, sublingual nifedipine is quite useful, as it is associated with a minimum of overshoot hypotension or serious side effects. Intravenous labetalol, diazoxide, or nitroprusside may also be used in the transplant patient with an accelerated phase of hypertension, just as it is used for such cases in non-transplant patients.

**ACE inhibitors.** When there is a question of renin-mediated hypertension due to diseased native kidneys, ACE inhibitors should be considered as more definitive therapy.<sup>21</sup> However, hypertension that is cyclosporine-mediated, associated with acute rejection, or aggravated by extracellular fluid volume expansion does not respond as well to ACE inhibitors. Thus, ACE inhibitors may not be very effective in the early post-transplant period, when the mechanism involved more frequently is related to these three factors.

This patient was considered a candidate for ACE inhibitor therapy because of the possibility that renin-mediated hypertension due to her diseased kidneys<sup>5</sup> was aggravating her hypertension several months after the transplant, when her renal function was relatively stable. The long-acting ACE inhibitor lisinopril was chosen because of the convenience of taking this medication once a day. This patient's reaction to lisinopril illustrates one of the potential side effects of ACE inhibitors in the presence of a solitary functioning kidney after transplantation. She exhibited immediate loss of renal function, and oliguria was noted within hours after the first dose of the medication. In such instances, the clini-

cian should be alert to the possibility of renal artery stenosis as the cause of hypertension.

In the presence of bilateral renal artery stenosis in a non-transplant patient and stenosis to a solitary kidney, the glomerular filtration rate is dependent upon the local effects of the renin-angiotensin system on the efferent arteriole of the nephron.<sup>23,24</sup> Glomerular capillary pressure is maintained at a normal rate in this pathologic situation of decreased perfusion pressure to the kidney via preferential vasoconstriction of the efferent arteriole compared to the afferent arteriole. Preferential efferent vasoconstriction occurs because of the local production of renin and angiotensin in the juxtaglomerular apparatus of the nephron. When an ACE inhibitor is added to the therapeutic regimen, angiotensin I is not converted to angiotensin II locally in the kidney, resulting in preferential vasodilatation of the efferent arteriole. Blood is shunted through the glomerular capillary, glomerular capillary pressure decreases, and the glomerular filtration rate drops abruptly.

This physiologic effect was seen in this patient when oligo-anuria abruptly developed after one dose of lisinopril. Her prolonged acute renal failure was probably due to the drug's long duration of action. Since lisinopril is excreted by the kidneys, blood levels of the drug may have remained elevated for several days after a single dose. The patient improved as a result of hemodialysis that may have removed the drug, thus allowing the local renin-angiotensin system to return to normal. A short-acting ACE inhibitor such as captopril may be used as a test dose to assess the response in a patient who may have renal artery stenosis to a solitary kidney.

It is essential that transplant recipients have their renal function assessed by urine output and their serum creatinine levels monitored shortly after ACE inhibitor therapy is initiated and periodically thereafter. The clinical feature that often raises a suspicion of renal artery stenosis is worsening of the glomerular filtration rate, which is usually assessed by an increase in the serum creatinine level associated with ACE inhibitor therapy. Although this sequence of events may occur suddenly, as happened in this patient, other patients may exhibit a more indolent rise in the serum creatinine levels days or weeks after therapy is started. Renal artery stenosis should be considered for any patient who has such a loss of renal function associated with ACE inhibitor therapy.

### Renal artery stenosis

**Etiology.** Because the etiology of renal artery stenosis is multifactorial,<sup>25</sup> it is often difficult to determine the

exact cause for the stenosis. Technical problems with the anastomosis may cause stenosis, especially if an end-to-end anastomosis to the internal iliac artery was performed. Other possible causes include rejection involving the transplanted renal artery that may lead to intimal thickening, activation of platelets and the coagulation system, torsion on the vessel due to the anatomic location of the kidney in relation to the vessels, injury to the transplanted renal artery at the time of harvesting or preservation (especially if the artery is cannulated), and extrinsic compression due to scarring around the hilum of the kidney. In addition, symptomatic renal artery stenosis may be caused by atherosclerosis in the native vessels proximal to the anastomosis or in the transplanted renal artery.

**Diagnosis by digital subtraction angiography.** A variety of screening tests have been suggested for the diagnosis of renal artery stenosis, including intravenous digital subtraction angiography (DSA), nuclear renal scans, peripheral renin activity or response of peripheral renin activity to a challenge dose of an ACE inhibitor, and intravenous pyelography. However, none of these tests has proven definitive in most renal transplant patients. The preferential test to diagnose this problem is intra-arterial DSA. The arterial anatomy can be delineated clearly in order to determine the presence or absence of arterial stenosis to the transplanted kidney (Figure 1). With this technique, the amount of contrast material can be limited, and the catheter is smaller than that used for conventional angiography. In experienced hands, this test carries a minimal risk of morbidity.

**Clinical management of renal artery stenosis.** Therapeutic intervention must be considered if the patient's clinical course indicates that the stenosis is functionally significant. As mentioned above, worsening renal function associated with ACE inhibitor therapy is one problem encountered clinically in patients who have renal artery stenosis to a solitary kidney. Other problems are refractory and difficult-to-control hypertension with large fluctuations of blood pressure associated with aggressive pharmacological therapy and volume depletion. Since this situation is similar to the model of one-kidney, one-clip hypertension in the rat, hypertension may be either renin-mediated, as is the case early in the animal model, or it may be more salt- and volume-mediated, as occurs later in the animal model. Poor renal perfusion secondary to renal artery stenosis to the solitary kidney leads to severe salt and water retention. If sodium intake is not restricted, extracellular fluid volume expansion may sometimes be severe and refractory to treatment.<sup>26</sup> As a result, the blood pressure response to



pharmacologic agents worsens, and fluid overload may develop, leading to edema and congestive heart failure. Patients generally do not respond well to diuretics and may need high doses of loop diuretics or combination therapy with diuretics affecting different segments of the nephron; for example, thiazide-type diuretics combined with loop diuretics, sometimes further combined with potassium-sparing agents.

The typical clinical scenario of difficult-to-control hypertension in patients who have renal artery stenosis to a solitary kidney is recurrent episodes of fluid overload and congestive heart failure interspersed with volume depletion, postural hypotension, and prerenal azotemia. If an ACE inhibitor then causes renal function to deteriorate, the diagnosis is almost certain.

*Percutaneous transluminal renal angioplasty.* Although asymptomatic renal artery stenosis may not require intervention, usually the diagnosis is not made until clinical problems associated with the stenosis become manifest and intervention is warranted. PTRAs have been performed at our center and others successfully in this situation.<sup>27</sup> Although the procedure entails some risk of trauma to the artery (dissection, thrombosis, and possibly graft loss), the incidence of these complications is probably lower than with an open surgical procedure. Compared to patients with renal artery stenosis of the native kidney, surgery on the transplanted kidney is more complicated because of the previous surgical pro-

cedure and scarring that may have occurred. If PTRAs fail, surgical revascularization is a last resort.<sup>28,29</sup> Although PTRAs are often successful in relieving the stenosis, stenosis may recur, and a repeat procedure or surgery may be required.

This patient underwent PTRAs successfully, and she has remained with mild hypertension easily controlled with a single agent. Her renal function is normal one year after transplantation. Renal artery stenosis has not recurred.

#### SUMMARY

Hypertension is a difficult clinical problem for patients who have received kidney transplantations. As was the case in this patient, the hypertension may be very difficult to control and lead to serious problems such as severe acute renal failure secondary to the institution of an ACE inhibitor. Generally, the most important factor affecting the long-term prognosis is the function of the transplanted kidney. If function remains relatively normal, hypertension can usually be controlled successfully as long as appropriate clinical decisions are made regarding its management.

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