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## Renal graft failure after addition of an angiotensin II receptor antagonist to an angiotensin-converting enzyme inhibitor: unmasking of an unknown iliac artery stenosis

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### Abstract

Combined treatment with an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin II (Ang II) receptor blocker (ARB) has been suggested in order to achieve a more complete blockade of the renin-angiotensin-aldosterone system in cardiovascular and renal disease. The present report describes a case of acute renal graft dysfunction following the addition of an ARB to existing ACE inhibition. This unmasked an unknown iliac artery stenosis. The case indicates a possible important role of Ang II generated by non-ACE pathways in this situation.

### Introduction

Systemic hypertension complicates the clinical course of most renal transplant patients. In chronic nephropathy, controlled studies have demonstrated that angiotensin-converting enzyme (ACE) inhibitors slow the progression of uraemia more effectively than conventional antihypertensive therapy.<sup>1-3</sup> There are no prospective controlled trials on the effects of ACE inhibition in renal transplantation, but ACE inhibitors (ACE-I), as well as angiotensin II receptor blockers (ARBs), are widely used in this setting. Recently, combined therapy with an ACE-I and an ARB was suggested, in order to achieve more complete blockade of the renin-angiotensin-aldosterone system (RAAS) in cardiovascular and renal disease.<sup>4</sup>

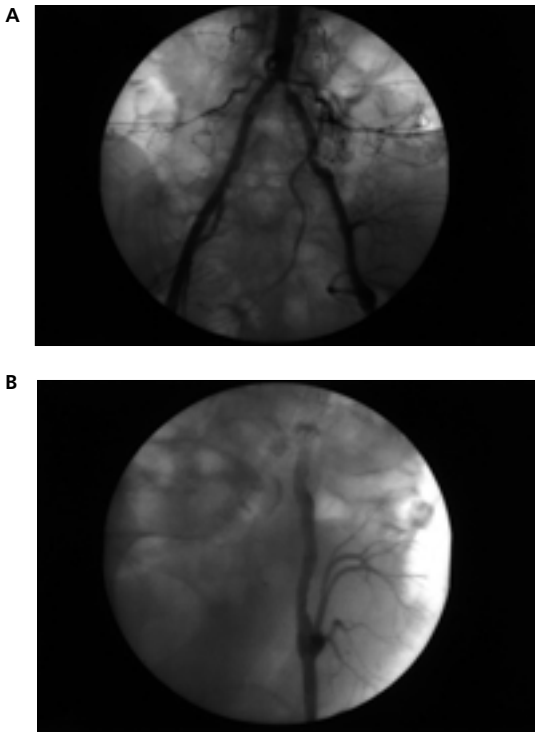
In patients with renal artery stenosis, ACE inhibition may cause decreased renal perfusion and a corresponding decline in glomerular filtration rate (GFR).<sup>5,6</sup> The present case report describes a renal transplant patient who developed graft dysfunction when an ARB was added to existing ACE inhibition. This led to the diagnosis and treatment of a stenosis of the common iliac artery, acting as a functional renal graft artery stenosis. The pathophysiological mechanism might be more complete inhibition of the RAAS by the combined therapy.

### Case report

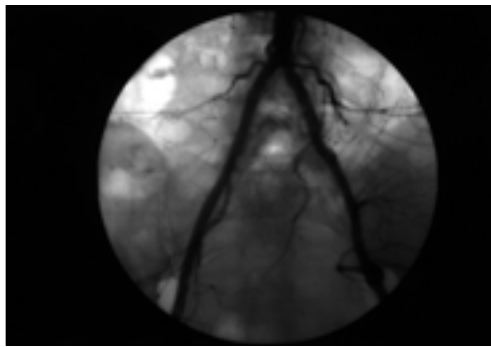
A 48-year-old female renal transplant patient was admitted to Herlev Hospital in April 2000 because of a marked increase in plasma creatinine. The patient had a history of Type 1 diabetes mellitus from the age of 14 years, arterial hypertension, and diabetic nephropathy with end-stage renal failure

in 1991. She had been on peritoneal dialysis until a cadaveric renal transplantation was performed in 1994. The kidney had been transplanted into the left iliac fossa with end-to-side anastomosis of two combined graft arteries to the external iliac artery, which had shown moderate arteriosclerosis at the time of transplantation. The post-transplantation course had been uncomplicated, with no rejection episodes. Antihypertensive treatment with an ACE-I, enalapril 10 mg daily, and frusemide had been started one month after transplantation, because of high blood pressure (BP), and this had been associated with a minor transient rise in plasma creatinine, which thereafter stabilised at around 150 µmol/l. In 1996, her BP was poorly controlled and therapy was supplemented with diltiazem. Late in 1998, her BP had increased to a level of 190/105 mmHg, and, in January 1999, enalapril was changed to the ARB, candesartan. This had no effect on the BP, but a minor increase in plasma creatinine to around 175 µmol/l was observed. Captopril renography in March 1999 had not suggested renovascular disease. After five months, candesartan was stopped and enalapril re-started. Her BP remained somewhat high and, in March 2000, candesartan 8 mg daily was added to the enalapril therapy in order to achieve better BP control. This was followed by a marked rise in plasma creatinine from 173 to 311 µmol/l and the patient was admitted to hospital. Doppler-ultrasonography demonstrated normal morphology and perfusion of the graft, a resistance index of 0.6-0.7, and no dilation of the urinary outflow tract. Renal graft biopsy did not show any acute rejection. Candesartan was stopped and plasma creatinine fell gradually during ongoing enalapril administration. Graft artery stenosis was suspected and magnetic resonance angiography was performed. The angiogram showed bilateral stenoses of the common iliac arteries. On the left side, a severe stenosis was located immediately distal to the aorta (Figure 1A). There was no graft artery stenosis (Figure 1B). On inquiry, the patient admitted to having claudication of the left extremity. A percutaneous transluminal angioplasty, with bilateral stenting of the iliac artery stenoses, was performed (Figure 2). Thereafter, plasma creatinine decreased further and arterial BP became well regulated. The

**Figure 1** Angiogram demonstrating bilateral stenoses in the common iliac arteries, primarily left-sided (A). Angiogram magnification at the graft artery anastomosis excluding graft artery stenosis (B).



**Figure 2** Angiogram after percutaneous transluminal angioplasty with bilateral stenting of iliac artery stenoses (kissing stents).

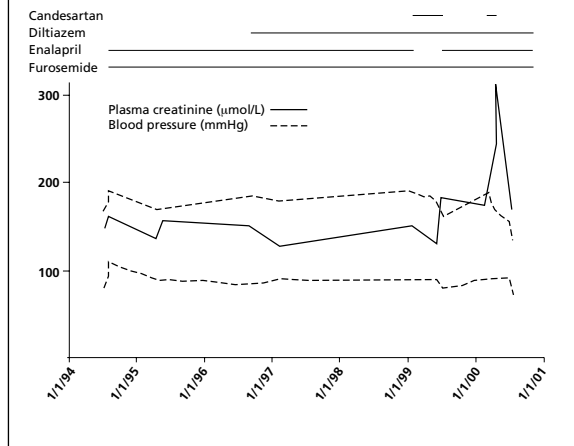


changes in plasma creatinine, BP and antihypertensive drugs are shown in Figure 3. Other medications included steroids, azathioprine, cyclosporine A and acetylsalicylic acid. Blood cyclosporine levels remained within the therapeutic level during the whole course.

**Discussion**

In renal hypoperfusion, as in renal artery stenosis, the glomerular hydrostatic pressure, and thereby GFR, is maintained in part by angiotensin II (Ang II)-mediated constriction of the postglomerular efferent arteriole. In this setting, blockade of the

**Figure 3** Changes in plasma creatinine, blood pressure and antihypertensive therapy.



RAAS by ACE inhibition may lead to a decrease in GFR.<sup>5,6</sup> The influence of ARBs in renovascular disease has not been clarified. Long-term ACE inhibition results in incomplete blockade of the RAAS, as plasma Ang II and aldosterone concentrations return back to control levels, owing to Ang II generation by ACE-independent enzymatic pathways, a phenomenon called ACE-escape. It has therefore been suggested that combined therapy with an ACE-I and an ARB might result in more complete blockade, by interruption of the RAAS at different sites. This might be beneficial for the treatment of hypertension, cardiac failure and progressive chronic nephropathy.<sup>4,7-9</sup> In the present case, the patient had an unknown functional renal graft artery stenosis. ACE-I therapy had been given and tolerated for several years. The dose of enalapril was adjusted according to renal function, as the drug is renally excreted. In patients with chronic renal failure, we have recently demonstrated that a median dose of 10 mg enalapril was associated with trough serum concentrations of enalaprilat which were markedly higher than those seen in hypertensive subjects with normal renal function.<sup>10</sup> It cannot be excluded that an increase in the dose of enalapril, rather than addition of an ARB, might also have resulted in a decline in renal function. However, it might be assumed that the stenosis had developed during ongoing ACE-I treatment and that the renal graft function had been maintained by Ang II generated by non-ACE pathways. Ang II receptor blockade inhibits the actions of Ang II, regardless of its source and therefore the addition of this treatment to existing ACE inhibition in the present case caused a critical fall in renal graft function.

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