Angiotensin-Converting Enzyme Inhibitor-Induced Renal Failure: Causes, Consequences, and Diagnostic Uses

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ABSTRACT
Angiotensin-converting enzyme inhibitor-induced renal failure is now a well-recognized phenomenon that appears to occur almost exclusively in patients with a preexisting reduction in renal perfusion pressure, especially those with renovascular disease. In the latter group of patients, renal failure probably results from some combination of reduced poststenotic renal perfusion pressure and a unique disturbance in the autoregulation of glomerular filtration rate. Although traditionally regarded as functional and reversible, recent animal studies suggest that angiotensin-converting enzyme inhibitor-induced reductions of glomerular filtration rate may lead to progressive renal atrophy, an observation that raises concerns about the safety of these agents in patients with renovascular disease. This changing pattern in clinical indications for the use of ACE inhibitors can be attributed, in part, to the discovery that these drugs affect renal function in a manner that varies considerably depending on the underlying degree of renal impairment and the preexisting level of renal perfusion pressure. The potentially salutary effects of ACE inhibition on the renal function of patients with essential and renal parenchymal hypertension have been the subject of a number of studies and reviews (1–5). This report focuses on the deleterious consequences of ACE inhibition in patients with renovascular disease. Shortly after the introduction of captopril in the late 1970s, a syndrome of acute reversible renal failure was described in anecdotal case reports and in small series of patients receiving ACE inhibitors (6–16). In typical cases, renal insufficiency reversed rapidly after withdrawal of the offending drug, indicating a functional, rather than a nephrotoxic, basis for the decline in glomerular filtration rate (GFR). By 1984, the cumulative experience suggested that this syndrome occurs almost exclusively in patients with bilateral renal-artery stenoses or renal artery stenosis in a solitary kidney. A similar, albeit less dramatic, syndrome was described later in patients with severe, low-output cardiac failure (17), suggesting that a preexisting reduction in renal perfusion pressure is a common, if not prerequisite, pathophysiologic feature. Subsequent studies have shown that ACE inhibitors also may induce a reduction of GFR in the stenotic kidneys of subjects with unilateral renal artery stenosis (18,19). In such cases, the
compensatory hyperfiltration in the contralateral kidney. The long-term consequences of this ipsilateral hypofiltration and contralateral hyperfiltration remain to be determined. However, the observation that these hemodynamic alterations occur predictably after as little as a single dose of an ACE inhibitor provides a basis for the growing use of ACE inhibitors as adjuncts in the diagnosis of RVHT. Thus, an adverse consequence of therapy with ACE inhibitors has evolved into a potentially valuable diagnostic aid. It is timely to review the speculated mechanisms and consequences of ACE inhibitor-induced renal failure in patients with renovascular disease as a background to a discussion of the use of these agents in the diagnosis of RVHT.

MECHANISMS OF ACE INHIBITOR-INDUCED RENAL FAILURE IN RENOVASCULAR DISEASE

Dissociation in the Autoregulation of Glomerular Filtration and Renal Blood Flow

Several years before clinical descriptions of ACE inhibitor-induced renal failure, a pathophysiologic basis for the phenomenon was delineated by experiments originally designed to examine the influence of the renin-angiotensin system on the autoregulation of renal blood flow (RBF) and GFR. In normal and sodium-depleted animals, RBF, GFR, and filtration fraction remain relatively constant over a wide range of experimentally manipulated renal perfusion pressures. As perfusion pressure is reduced gradually, the initial, dominant renal autoregulatory response is afferent arteriolar dilation (20,21). With further reduction of perfusion pressure to the lower end of the autoregulatory range, glomerular capillary pressure and GFR are sustained, in addition, by a progressive increase in efferent arteriolar resistance (22). Together with the previous observation that a reduction in renal artery perfusion pressure stimulates the release of renin (23), these findings suggested that, in the presence of reduced renal perfusion pressure, the renin-angiotensin system may participate in the autoregulation of GFR via an efferent arteriolar constrictor mechanism. An increase in the intrarenal formation of angiotensin II during reductions in renal perfusion pressure could help to maintain efferent arteriolar tone and effective filtration pressure despite the expected activation of well-known vasodilator mechanisms (mediated by a myogenic response or by tubuloglomerular feedback) that would tend to dilate both afferent and efferent arterioles.

To test this hypothesis, Hall and co-workers (22, 24, 25) studied the autoregulation of RBF and GFR in dogs subjected to suprarenal aortic clamping under a variety of experimental conditions designed to suppress the activity of the renin-angiotensin system. These conditions included a state of renin depletion induced by salt loading and administration of deoxycorticosterone acetate (22), administration of a competitive inhibitor of angiotensin II ([Sar1, Ile8]angiotensin II) (24), and infusion of an ACE inhibitor (SQ 20881) (25). When renal perfusion pressure is lowered under any of these conditions, a dissociation in the autoregulation of RBF and GFR occurs; GFR decreases while RBF is modestly increased, resulting in a dramatic reduction of filtration fraction (Figure 1). Moreover, efferent arteriolar resistance (calculated by indirect methods) declines (Figure 2). These observations indicated that, under circumstances in

Figure 1. Effect of reducing renal artery pressure (RAP) on RBF, GFR, and filtration fraction (FF), expressed as percentage of control values in normal dogs (solid lines) and dogs subjected to renin-angiotensin blockade (dashed lines). (From ref. 22 with permission).
which renal perfusion pressure is reduced, transcapillary hydraulic pressures that drive glomerular filtration are sustained by a preferential increase in postglomerular efferent resistance maintained by angiotensin II. ACE inhibition and other maneuvers that suppress the renin-angiotensin system block the formation or action of angiotensin II, reduce postglomerular resistance, and reduce transcapillary forces driving filtration so that GFR decreases. At the same time, RBF is preserved or increased because of the reduction in efferent arteriolar tone and a simultaneous reduction in afferent arteriolar tone mediated by other vasodilatory mechanisms.

Extrapolating from the above experimental model, the generation of a functional form of renal failure may be anticipated when the renin-angiotensin system is blocked and the entire renal mass is perfused at a sufficiently low pressure. This set of conditions is satisfied when an ACE inhibitor is administered to patients with hemodynamically severe renal artery stenosis involving either both renal arteries or the renal artery of a solitary kidney, whether native or transplanted. According to the canine model described above, this functional form of acute renal failure would differ from other more familiar forms of "prerenal" azotemia, being characterized by glomerular hypofiltration and a relative increase in renal plasma flow.

In contrast to circumstances in which there is preexisting global renal hypoperfusion, administration of ACE inhibitors to patients with normal renal arteries would not be expected to result in such functional reductions of GFR because, unless critical systemic hypotension develops, renal artery perfusion pressure should remain within the range in which autoregulation of GFR is not dependent on an intact renin-angiotensin system. Clinically evident reductions in GFR also would not be anticipated when ACE inhibitors are administered to patients with unilateral renal artery stenosis and a well-preserved normal contralateral kidney. By using a rat model of two-kidney, one-clip RVHT, Huang et al. (18,26) demonstrated that acute renin-angiotensin blockade results in a reversible decrease in GFR in the clipped kidney and a simultaneous increase in both RBF and GFR in the unclipped kidney (Figure 3). If this phenomenon occurs in patients with unilateral renal artery stenosis, total renal function (as assessed by serum creatinine values or other measurements of total GFR) may change little in response to ACE inhibition, despite a profound reduction of GFR in the stenosed kidney.

**Reduction in Renal Perfusion Pressure With Failure to Autoregulate RBF**

A dissociation in the autoregulation of GFR and RBF need not be invoked as an explanation for ACE inhibitor-induced renal failure. Micropuncture studies in rats have demonstrated that filtration pressure equilibrium is achieved at the efferent end of the glomerular capillary when glomerular plasma flow is low; under such circumstances, GFR is dependent on RBF (27). Presuming that filtration equilibrium occurs in humans, the GFR of an underperfused kidney with renal artery stenosis should be dependent on RBF. Even a modest reduction in systemic pressure could reduce poststenotic perfusion pressure to a low level at which the autoregulation of RBF fails, resulting in a concomitant decrease in GFR. Supporting this hypothesis, Textor et al. (28) administered intravenous sodium nitroprusside to patients with bilateral renal artery stenoses and demonstrated that a moderate reduction of systemic blood pressure by this vasodilator can reduce poststenotic perfusion pressure to a critical level beyond which autoregula-
Figure 3. Responses of GFR, filtration fraction, and urine flow of the clipped kidney (solid dots) and the nonclipped kidney (open circles) during infusion of the converting enzyme inhibitor SQ20881 and subsequent unclipping in a two-kidney, one-clip model of hypertension. Symbols are: *P < 0.05; **P < 0.01; ***P < 0.001 when compared with control period; †P < 0.05; ††P < 0.01; †††P < 0.001 when the unclipping is compared with the last period of SQ20881 infusion. (From ref. 18 with permission).

Figure 4. Changes in blood pressure (BP), effective renal plasma flow (ERPF), and GFR during intravenous infusion of sodium nitroprusside in eight patients with bilateral renal artery stenosis. Double asterisks indicate P < 0.01 and the single asterisk indicates P < 0.05, comparing values during and before infusion. (From ref. 28 with permission).

The nitroprusside infusion and could not be duplicated after surgical correction of the stenoses. Whether this interesting phenomenon observed during treatment with nitroprusside is applicable to all antihypertensive agents has been open to question. Ying et al. (29) reported two cases of acute reversible renal failure in patients with renal artery stenosis in a solitary kidney while receiving either minoxidil or a combination of methyldopa, nifedipine, nitrates, and furosemide. However, Ribstein et al. (30) administered nifedipine to 22 patients with either bilateral renal artery stenoses or stenosis in a solitary kidney and noted a 13% increase in GFR and no change in renal plasma flow, despite a 19% reduction in mean arterial pressure. Similar observations by others (31,32) suggest that this calcium channel blocker may be unique in protecting intraglomerular pressure in the face of declining renal perfusion pressure.

Because the ACE inhibitors are particularly effective in reducing systemic blood pressure in RVHT, a critical reduction of poststenotic perfusion pressure could account for ACE inhibitor-induced renal failure in some cases. A number of investigators have noted a poor correlation between the fall in systemic pressure and the change in GFR induced by ACE inhibitors (3,10,16); however, subtle changes in perfusion pressure in response to small decrements in systemic blood pressure may still play a role in the development of ACE inhibitor-induced renal failure. Indeed, while most clinical studies of ACE inhibitor-induced severe
renal failure confirm the decline in GFR and filtration fraction predicted by the canine model described above, many report a decrease, rather than the predicted increase, in RBF (15,33–35), suggesting that renal perfusion pressure declines in many cases.

On the other hand, subjects with ACE inhibitor-induced renal failure do not routinely develop renal failure when systemic pressure is lowered by other antihypertensive agents to levels comparable to those achieved with ACE inhibitors. Helmchen et al. (36) administered captopril, dihydralazine, or minoxidil to rats with two-kidney, two-clip RVHT and found that, despite comparable reductions in mean arterial pressure, only captopril induced acute renal failure. In the clinical study of Ribstein et al. (30), administration of captopril to patients with bilateral renal artery stenoses or stenosis in a solitary kidney produced only a 7% reduction in mean arterial pressure and a 23% reduction in GFR, contrasting sharply with the response to nifedipine in the same patients (see above). Comparing the effects of captopril to sodium nitroprusside in patients with unilateral renal artery stenosis, Textor et al. (37) also demonstrated that, with comparable reductions of systemic blood pressure, only the ACE inhibitor induced a significant decrease in GFR. These observations suggest that a disturbance in the autoregulation of GFR mediated by the loss of angiotensin II-mediated efferent arteriolar tone is probably more important than any accompanying reduction in renal perfusion pressure in the pathophysiology of ACE inhibitor-induced renal failure.

The two mechanisms outlined above may not be mutually exclusive. In the presence of reduced renal perfusion pressure, loss of efferent arteriolar tone would still exaggerate any decline in GFR. Still, the mechanisms differ substantially in their potential effects on the preservation of renal function during long-term ACE inhibition in patients with RVHT. According to the first theory, ACE inhibition results in hypofiltration and preserved or increased RBF. If perfusion pressure and RBF decline during ACE inhibition, the effects of hypofiltration are compounded by the effects of additional renal ischemia.

The Role of Sodium Balance

Several lines of evidence suggest that sodium depletion can accentuate or precipitate ACE inhibitor-induced renal failure in patients with RVHT. In the dog model, autoregulation of RBF and GFR are maintained under conditions of sodium depletion (24); however, the failure to autoregulate GFR during pharmacologic blockade of the renin-angiotensin system is exaggerated by prior sodium depletion (22,24). The early observation that many patients with ACE inhibitor-induced renal failure were concomitantly receiving diuretics prompted the suggestion that diuretic-induced sodium depletion may be a risk factor for the clinical syndrome (16). A number of clinical reports describe patients with known renovascular disease in whom renal function deteriorated during treatment with the combination of an ACE inhibitor and a diuretic but not with the ACE inhibitor alone (38–41). In many of these cases, renal failure resolved rapidly upon discontinuation of the diuretic, despite continued treatment with the ACE inhibitor (38). McMurray and Matthews (42) described three patients receiving ACE inhibitors in whom acute renal failure developed only after intercurrent gastrointestinal fluid losses. In a single patient with transplant renal artery stenosis, it was shown that administration of a single dose of captopril could precipitate acute renal failure under conditions of sodium depletion induced by dietary salt restriction and diuretic therapy, while an identical dose of the drug had no clinically evident effect on renal function after sodium repletion (43).

Taken together, these observations suggest that sodium depletion may increase the dependency of GFR on an intact renin-angiotensin system and may sensitize susceptible patients to the development of renal failure after ACE inhibition. A reduction in the density of efferent arteriolar angiotensin II receptors under conditions of sodium depletion could account for this effect. In rats with two-kidney, one-clip RVHT, Schiffrin et al. (44) demonstrated that 10 days of dietary sodium restriction produced a significant decrease in the concentration of angiotensin II receptors in a particular fraction of the mesenteric artery, presumably due to homologous downregulation induced by elevated levels of angiotensin II. A similar reduction in the number of angiotensin II receptors in the efferent arteriole could potentiate the detrimental effects of ACE blockade on GFR. Because sodium depletion accentuates the antihypertensive effect of ACE inhibitors, it is possible that exaggerated hypotension and reduced renal perfusion pressure explain the interaction between sodium depletion and ACE inhibition in some cases. Andreucci et al. (45) have postulated further that natriuresis induced by the ACE inhibitors themselves may play a pivotal role in reducing GFR in patients with RVHT. On the basis of the observation that high doses of captopril increase the renal excretion of prostaglandins (46), these authors speculated that prostaglandin-mediated natriuresis and volume contraction are responsible for the syndrome of ACE inhibitor-induced renal failure. Their hypothesis was supported by the finding that salt loading or administration of aspirin prevented the development of renal failure, despite continued administration of captopril (45).

Although the exact mechanisms remain unknown, the data suggest that sodium depletion is an important factor in the clinical expression of ACE inhibitor-induced renal failure. Attenuation of the adverse
renal hemodynamic effects of ACE inhibitors after sodium repletion may account for the observation that ACE inhibitor-induced renal failure can be reversed in some cases simply by discontinuing concomitant diuretic therapy. Moreover, the absence of renal insufficiency in sodium-replete patients receiving ACE inhibitors should not exclude the possibility of underlying renovascular disease.

CLINICAL CONSEQUENCES OF ACE INHIBITION IN RENOVASCULAR DISEASE

Acute Renal Failure

The incidence of significant azotemia complicating therapy with ACE inhibitors in patients with renovascular disease is uncertain. Even among high-risk patients with angiographically documented bilateral renal artery stenoses or renal artery stenosis in a solitary kidney, clinically evident acute renal failure resulting from treatment with ACE inhibitors is relatively uncommon. In a retrospective analysis of 136 such patients, Hollenberg (47) reported only a 6% incidence of captopril-induced renal failure if sufficient severity to warrant discontinuation of therapy; however, 70 of these patients, including 33 with unilateral renal artery stenosis, showed a significant increase in serum creatinine concentration (more than 0.3 mg/dL) (47). Judged by an acute rise in serum creatinine to three times basal level or to more than 9 mg/dL, Jackson et al. (48) observed captopril-induced renal failure in 23% of patients with bilateral renal artery stenoses and in 38% of patients with solitary renal artery stenosis. In a prospective trial of therapy with enalapril and hydrochlorothiazide in 22 patients with unilateral and 14 patients with bilateral renal artery stenoses, Franklin and Smith (49) noted a rise in serum creatinine of more than 0.3 mg/dL in 20% of the patients (49). Interestingly, 7 of 10 patients exhibiting a rise in serum creatinine had unilateral and not bilateral lesions, suggesting that ACE inhibition-induced reductions of GFR in a unilaterally stenotic kidney may not be fully balanced by a rise in GFR of the normal contralateral kidney. This phenomenon might be anticipated in patients with long-standing unilateral RVHT if the renal reserve of the normal contralateral kidney has been compromised by prolonged hypertension and arteriolar nephrosclerosis. The absence of renal failure in apparently high-risk patients with angiographic evidence of renovascular disease has raised doubts about the applicability of anecdotal reports to all cases of RVHT (50–52). The reasons for the inconsistent occurrence of acute renal dysfunction during ACE inhibition in patients at risk remain unclear. However, limitations in the sensitivity and specificity of angiography, variations in the grade of severity of the stenoses, sodium and volume status (see above), and the balance of prevailing vasoactive substances (e.g., prostaglandins, kinins, catecholamines) figure as important variables.

Despite the relative rarity of clinically evident ACE inhibitor-induced renal failure, it remains prudent to recommend that the development of otherwise unexplained azotemia in a patient receiving an ACE inhibitor should raise the suspicion of underlying renovascular disease. Isolated case reports have described renal failure associated with ACE inhibition in patients with angiographically normal renal arteries (53–55). Murphy et al. (54) suggested that this phenomenon can occur in patients with diffuse small vessel disease and normal renal arteries. Acute tubular necrosis can complicate therapy with any antihypertensive agent if severe hypotension occurs, even in the absence of renal artery stenosis. In addition, sporadic reports have implicated ACE inhibitors as a cause of acute interstitial nephritis and/or renal tubular dysfunction (56–59). Interpretation of these cases is confounded by lack of histologic confirmation, concurrent exposure to other nephrotoxic drugs, or failure to exclude the presence of renal artery stenosis. Excluding these exceptional cases and perhaps patients with severe heart failure, the literature supports the notion that, in the vast majority of cases, ACE inhibitor-induced renal failure occurs in patients with renovascular disease.

In contrast to the low frequency of ACE inhibitor-induced renal failure judged by the presence of azotemia, studies employing clearance or scintigraphic techniques suggest that at least subclinical reductions of GFR are common during ACE inhibition in patients with both unilateral and bilateral renal artery stenoses. By using creatinine clearance as an estimate of GFR, Ribstein et al. (30) demonstrated a more than 20% reduction of GFR in 8 of 10 patients with renal artery stenosis in a solitary kidney and in 5 of 12 patients with bilateral renal artery stenoses. Jackson et al. (60) used the clearance of Tc-99m-diylenetetramine pentaacetic acid (DTPA) and demonstrated a mean 33% reduction of GFR in five of five patients with bilateral renal artery stenoses, only three of whom exhibited a clinically significant rise in serum creatinine concentration. More strikingly incongruous with the low clinical estimates of the frequency of ACE inhibitor-induced renal failure are observations from split renal function studies of patients with unilateral renal artery stenosis which suggest that alterations in hemodynamics occur in the stenosed kidney with great regularity. Hodsman et al. (52) performed split isotopic measurements of renal plasma flow in 10 patients with unilateral renal artery stenosis treated with enalapril for 3 months and demonstrated reduced renal plasma flow on the affected side in all patients. Mean plasma flow to the affected side fell significantly from 163 to 102 mL/min while increasing from 298 to 437 mL/min on
the unaffected side. After 3 months of therapy, mean serum creatinine had risen from 1.2 to 1.4 mg/dL. Wenting et al. (19) reported a unilateral decline in \(^{125}\)I-halothane clearance in 7 of 14 captopril-treated patients with angiographically documented unilateral renal artery stenosis. In 16 patients with unilateral stenosis, Jackson et al. (60) showed no change in total DTPA clearance; however, split renal function studies demonstrated a mean 7.5 mL/min decline in GFR in the stenosed kidneys with a mean 8.2 mL/min rise in GFR on the nonstenosed side (60). Similarly, Miyamori et al. (61) detected only a slight decrease in overall GFR after 48 weeks of captopril treatment in three of five patients with unilateral stenosis; however, split renal function studies showed that captopril induced a fall in GFR of the stenotic kidney, with no change in function on the intact side (61).

Because a subclinical reduction of GFR occurs more commonly than does clinically evident acute renal failure, it is not surprising that the clinical presentation of ACE inhibitor-induced renal failure is variable, ranging from transient anuria to a trivial, often unrecognized rise in serum creatinine concentration. Patients with renovascular disease at particular risk for the development of azotemic ACE Inhibitor-induced renal failure are those concurrently receiving diuretics and those with preexisting azotemia (16,47), the latter probably reflecting the severity of the underlying renovascular disease. In the majority of reported cases, patients remain nonoliguric. Characteristics of the urine differ sharply from the indices typical of acute tubular necrosis: urine specific gravity and osmolality are increased, and urine sodium concentration is low in the absence of diuretic therapy (2,9). Azotemia remits predictably and rapidly when the ACE inhibitor is stopped or, in some cases, when the dose is reduced. Complete recovery generally occurs in less than 2 weeks in the case of patients given captopril (15,16) but may be delayed in patients receiving the longer-acting ACE inhibitors or in those with persistent volume depletion.

As noted earlier, discontinuation of diuretics or sodium loading may hasten recovery from ACE inhibitor-induced renal failure. There is currently no consensus about the absolute need to discontinue the ACE inhibitor in patients with this syndrome. Dose reduction with or without discontinuation of therapy may provide adequate control of systemic hypertension and resolution of azotemia. However, on the basis of considerations outlined below, we believe that it may be dangerous to continue ACE inhibition in such patients.

**Progressive Renal Atrophy**

Studies in animals have raised the serious concern that ACE inhibitor-induced renal failure may be neither functional nor entirely reversible. In their study of two-kidney, two-clip hypertension in rats, Helmchen et al. (36) showed that 4 days of treatment with captopril led to patchy tubular atrophy that was not duplicated in animals treated with other vasodilators. Grone and Helmchen (62) later confirmed the finding of proximal tubular atrophy after 14 days of treatment with enalapril in the clipped kidneys of rats with two-kidney, one-clip RVHT. These morphologic changes were not duplicated in similar rats receiving dihydralazine, despite comparable reductions of systemic pressure. Notably, enalapril caused a profound reduction of GFR in the clipped kidney while RBF was comparable to that observed in the control animals, suggesting that the tubular atrophy was not the result of renal ischemia per se. These observations prompted the investigators to speculate that the tubular changes represented a form of "disuse atrophy," a unique form of renal parenchymal disease resulting from hypofiltration and reduced tubular reabsorption in the absence of a reduction in RBF. In the same model, Michel et al. (63) treated rats with enalapril for 5 weeks and demonstrated tubular atrophy, interstitial fibrosis, and loss of kidney weight in clipped kidneys that far exceeded changes in an untreated control group. Jackson et al. (64) studied the effects of 12 months of enalapril, minoxidil, or no antihypertensive treatment in rats with two-kidney, one-clip RVHT and demonstrated irreversible fibrotic atrophy of the clipped kidney that was most pronounced in the enalapril-treated animals. RBF was not measured in either of the latter two studies, making it difficult to ascertain whether renal atrophy resulted from an isolated reduction in GFR (i.e., disuse atrophy) or from worsened renal ischemia.

The results of these animal studies should be extrapolated to human RVHT with caution. Disuse tubular atrophy has not been described in humans. In patients with the common forms of renovascular disease (atherosclerosis and fibromuscular dysplasia), it may be difficult to differentiate such a long-term detrimental effect of ACE inhibition from the renal atrophy that may be expected from progression of the underlying disease. Moreover, renal failure induced by ACE inhibition has been reported to reverse even after 2 years of treatment (65). Finally, any risk of potentiating renal atrophy may be limited to a minority of patients with RVHT and must be balanced against the proven efficacy of the ACE inhibitors in controlling systemic hypertension in a group of patients that is frequently resistant to other pharmacologic agents (66-68). While the risk of precipitating readily recognizable acute renal failure is highest among patients with bilateral renal artery stenoses or renal artery stenosis in a solitary kidney, any risk of chronic, unrecognized renal atrophy is
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paradoxically greatest in the much larger group of patients with unilateral disease because the normal contralateral kidney may mask untoward effects in the stenosed kidney. Just as concerning and even more unexplored are the long-term effects of relative hyperfusion and hyperfiltration that occur during ACE inhibition in the contralateral kidney of patients with unilateral RVHT. Further research is required to determine whether these concerns will ultimately make all forms of renovascular disease a relative contraindication for the use of ACE inhibitors.

Renal Thrombosis

Complete occlusion of a stenotic renal artery during treatment with an ACE inhibitor has been reported in a few patients with unilateral renal artery stenosis (69–71). It is difficult to prove that ACE inhibition per se contributed to the occlusion of the severely stenotic renal arteries since renal artery thrombosis is a well-recognized complication of progressive renovascular disease. Moreover, this complication may be anticipated when systemic pressure is abruptly lowered by any antihypertensive agent in the presence of severe renal stenosis and has been described, for example, in a patient receiving monotherapy with atenolol (72).

The Use of ACE Inhibitors in the Diagnosis of Renovascular Hypertension

Two phenomenon have stimulated renewed interest in screening for RVHT: (1) the development of percutaneous transluminal angioplasty, which offers the possibility of cure without surgery, and (2) recognition that the most common forms of renovascular disease (atherosclerosis and fibromuscular dysplasia) are progressive disorders that threaten renal function even when the associated hypertension is controlled pharmacologically (73,74). Conventional techniques such as intravenous pyelography, radioisotope renography, measurement of plasma renin activity (PRA), or determination of renal vein renin ratios have limited sensitivity and specificity as screening tests for RVHT. Even angiography, the gold standard for defining the anatomy of the renal arteries, by itself does not determine the functional significance of a renal artery stenosis. Largely on the basis of principles outlined above, the ACE inhibitors recently have been used adjunctively to enhance the sensitivity and specificity of conventional screening tests.

Blood Pressure Response to ACE Inhibition

Abrupt, first-dose hypotension resulting from administration of an ACE inhibitor has been correlated with pretreatment PRA levels (75,76). This observation raised the possibility that the blood pressure response to these agents could discriminate renin-dependent RVHT from essential and other forms of hypertension. Some studies support the notion that an exaggerated hypotensive response to an ACE inhibitor predicts not only the presence of RVHT, but also a favorable response to surgery or angioplasty (77,78). Subsequent large-scale studies, however, indicate a considerable overlap in the blood pressure response of patients with essential hypertension and those with RVHT (79,80), perhaps reflecting the wide variation in baseline PRA among patients with both essential hypertension and RVHT. The balance of data suggests that the change in blood pressure after administration of an ACE inhibitor does not discriminate well between renovascular and essential hypertension.

Stimulation of PRA by ACE Inhibitors

Even before mechanisms responsible for the auto-regulation of GFR in a hypoperfused kidney were fully elucidated, clinicians recognized that administration of ACE inhibitors to patients with RVHT caused a rise in peripheral PRA far greater than that observed in normal subjects or patients with essential hypertension. In 1978, Re et al. (81) demonstrated that ACE inhibition could accentuate the asymmetry of renal vein renin concentrations often found in patients with unilateral RVHT, suggesting that the stenotic kidney was the source of the reactive hyperreninemia. The cause of this enhanced renin production during ACE inhibition is not completely understood. Because angiotensin II directly inhibits the release of renin, loss of negative feedback by reduced generation of angiotensin II is the simplest explanation. Understanding that autoregulation of GFR is reduced simultaneously, an additional hypothesis is that the decline in GFR reduces delivery of sodium chloride to the distal nephron, thus stimulating release of renin by juxtaglomerular cells. Under normal circumstances, a ratio of renal venous PRA of 1.5 or greater (ipsilateral:contralateral) indicates physiologically significant renal artery stenosis and predicts improvement in blood pressure control after surgical revascularization or angioplasty (82,83). Maxwell et al. (84) have shown, however, that the use of this criterion results in false-negative tests in approximately 25% of patients. Several groups have demonstrated that stimulation with an ACE inhibitor may enhance the differential between renal vein renin levels and reduce the rate of false-negative tests (81,85–87). Thibonnier et al. (86) demonstrated that captopril-enhanced lateralization of renal vein renin levels predicted surgical curability in 6 of 18 patients deemed to be unoperable on the
basis of unstimulated studies. Lyons et al. (87) suggested that an ACE inhibitor-stimulated ratio of 3.0 or greater is highly predictive of surgical cure and may be elicited in patients whose prestimulation ratios are less than 1.5.

The marked hyperreninemic response to ACE inhibition in patients with RVHT forms the basis of a simpler test in which peripheral PRA is measured before and 60 min after administration of a small oral dose of captopril. In general, the dose employed is 25 to 50 mg; the tablets are crushed and dissolved in water to facilitate rapid oral absorption. After performing this test on more than 200 patients with various forms of hypertension, Muller et al. (79) developed the following criteria to differentiate RVHT from essential hypertension: (1) a 60-min post-captopril peripheral PRA of >12 ng/mL/h, (2) an absolute PRA increase of >10 ng/mL/h, or (3) a 150% increase in PRA (or 400% increase if baseline PRA is <3 ng/mL/h). It should be emphasized that these criteria were constructed retrospectively from an analysis of untreated, sodium-replete patients with normal renal function. Application of these criteria identified all patients with proven RVHT (100% sensitivity) with only a 2% rate of false-positive tests (98% specificity). Unfortunately, the test was neither as sensitive nor as specific in two important subsets of patients: those with renal insufficiency and those who required antihypertensive medications during the test—conditions that characterize many patients with resistant hypertension secondary to renovascular disease (88).

Some authors have confirmed the reliability of this test for RVHT in smaller numbers of patients (89–91); however, prospective applications of criteria similar to those described above by other investigators demonstrate a lower sensitivity and specificity with considerable overlap in the stimulated PRA of patients with RVHT and essential hypertension, especially in patients under the age of 40 years (92,93) (Figure 5). A direct comparison of the available studies is confounded by differences in the dose of captopril employed, criteria for a positive test, and definitions of angiographically significant renovascular disease. Although the test is relatively inexpensive, first-dose hypotension, sometimes requiring infusions with saline, can complicate the procedure, which prompted McCarthy and Weder (88) to suggest that the test should be reserved for clinical research protocols. The value of this test in screening for RVHT in an unselected population of hypertensives remains to be determined.

**Renography with ACE Inhibitors**

Early studies of split renal function during ACE inhibition in patients with unilateral RVHT provided the basis for renography with ACE inhibitors. In this promising method for detecting functionally significant RVHT, individual kidney function is assessed with radionuclide studies before and after the administration of an ACE inhibitor. The two radioisotopes most commonly employed for such studies are DTPA and [131I]jorthododihippurate (Hippuran). Renal handling of these isotopes generally is displayed by time-activity curves or scintiphotographic techniques. DTPA is excreted by the kidneys solely via glomerular filtration; however, because of the excellent imaging capabilities of its Tc-99m label, early phases of the DTPA study also may offer an index of renal perfusion. Hippuran is excreted both by glomerular filtration and tubular secretion such that its clearance is a marker for effective renal plasma flow. Like para-aminohippurate, the extraction ratio of Hippuran is very high, but its 131I label suffers from suboptimal imaging characteristics. Tc-99m-mercaptoacetyltriglycine, a new tracer with excellent imaging characteristics, is handled by the kidney in a fashion similar to para-aminohippurate and may offer an advantage over Hippuran in ACE inhibitor renography (94). Compared with baseline renograms, ACE inhibitor-induced renographic abnormalities that suggest renovascular disease include a reduction or delay in DTPA uptake (Figure 6) and a delay in Hippuran uptake compared with baseline studies.

### Figure 5. PRA in essential hypertension (EH) and renal artery stenosis (RAS) before and after an oral dose of 25 mg of captopril. Horizontal bars indicate mean values of the groups. (From ref. 93 with permission.)

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<td><strong>EH (n=76)</strong></td>
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<th></th>
<th>Baseline</th>
<th>Stimulated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EH (n=76)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.14 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Stimulated</td>
<td>0.28 (1)</td>
<td>0.56 (2)</td>
</tr>
<tr>
<td><strong>RAS (n=24)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>0.14 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Stimulated</td>
<td>0.28 (1)</td>
<td>0.56 (2)</td>
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</table>
excretion by the stenotic kidney (95–97). Uptake of Hippuran in the early phase of the renogram usually is unaffected, suggesting that RBF is preserved. Delayed washout of Hippuran probably results from cortical retention of the isotope resulting from the decline in GFR and urine flow in the affected kidney. DTPA is currently the tracer of choice to detect reductions of GFR after ACE inhibition in patients with normal renal function; however, Hippuran may be superior in patients with impaired renal function (98,99).

Majd et al. (100) first reported that captopril altered DTPA renograms in children with RVHT. A number of subsequent clinical studies suggest a high correlation between ACE inhibitor-induced renographic abnormalities and documented RVHT (80,98,101–109). The regularity with which ACE inhibitor renography predicts RVHT is remarkable considering that the protocols employed in such studies vary substantially with respect to the isotopes employed, the type and dose of ACE inhibitor used, the time delay between baseline and ACE inhibitor renographic studies, and the general preparation of the patient. Although intravenous enalaprilat has been used in an animal study (110), virtually all human studies have employed a 25- to 50-mg oral dose of captopril approximately 60 min before the renographic study. Kopecky et al. (111) have shown that furosemide augments the effects of captopril renography in rats with two-kidney, one-clip hypertension; however, most clinical investigators have chosen to hold diuretics and other antihypertensive agents and to water load their patients to assure a brisk flow of urine during the renographic study.

Variations in the reported sensitivity and specificity of ACE inhibitor renography (Table 1) can be attributed to differences in the dose of captopril used and the criteria for a positive test. In addition, most of the cited studies have been performed in referral centers and applied to patients with suspected or proven renovascular disease. The specificity of this test may be substantially lower when applied to an unselected population of hypertensive patients (105). Moreover, in all but one (109) of the studies summarized in Table 1, angiography was employed as the gold standard for a positive test. A more crucial issue is whether renography with ACE inhibitors can predict improvement or cure of hypertension with angioplasty or surgery. Nally et al. (80) reported abnormal DTPA renograms in 11 of 11 patients with documented RVHT and normal or equivocal renograms in 5 patients with essential hypertension. Three of seven patients with unilateral RVHT underwent angioplasty and exhibited improved blood pressure control. Fommei et al. (107) reported improvement of blood pressure control after surgery or angioplasty in nine of nine patients with positive captopril renography. Geyskes et al. (109) evaluated the predictive value of ACE inhibitor-stimulated DTPA renography in 21 patients with angiographically documented unilateral renovascular disease. Twelve of 15 patients who exhibited depressed ipsilateral uptake after ACE inhibition showed improved blood pressure after angioplasty (80% sensitivity). In contrast, six patients with no change in DTPA uptake had no improvement in blood pressure after technically successful angioplasty (100% specificity). Thus, a positive captopril renogram appears to be predictive of an improvement in blood pressure control after angioplasty (or surgery), whereas a negative study may
be predictive of little improvement after intervention in patients with angiographically apparent renal artery stenosis.

If these preliminary observations are confirmed by additional studies, ACE inhibitor renography clearly may affect clinical decision making, as determining the angiotensin II dependency of the hypertension appears to be more important in predicting the success of surgical intervention than simply documenting an anatomic lesion angiographically. Further work is required to standardize the criteria for a positive test, to determine the optimal type and dose of an ACE inhibitor, and to further differentiate the utility of various radionuclides. In addition, available data are too limited to judge the predictive value of ACE inhibitor renography in patients with bilateral renal artery stenoses, branch stenoses, or severe renal impairment. It seems unlikely that renography with ACE inhibitors or measurements of ACE inhibitor-stimulated PRA will prove to be cost effective in screening large patient populations for RVHT. However, the preliminary observations outlined above suggest that such tests, particularly ACE inhibitor renography, may ultimately prove to be useful in judging the functional significance of angiographically documented renovascular disease.

REFERENCES


### TABLE 1. Sensitivity and specificity of captopril renography in predicting renovascular hypertension

<table>
<thead>
<tr>
<th>Authors (reference no.)</th>
<th>No. of Patients with RAS</th>
<th>No. of Patients with EH</th>
<th>Captopril Dose (mg)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<td>Nally et al. (80)</td>
<td>11</td>
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<td>17</td>
<td>25</td>
<td>93</td>
<td>96</td>
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</table>

*RAS, renal artery stenosis; EH, essential hypertension.*
ACE Inhibition in Renovascular Disease


