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What ACE inhibitor-induced changes in serum creatinine tell us about a possible diagnosis of renal artery stenosis

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ABSTRACT In renal artery stenosis, GFR becomes angiotensin II-dependent and therefore sensitive to ACE inhibitor. However, the effect of ACE inhibitor on SCr in the presence of RAS is complicated by several factors: serum creatinine is a poor indicator of GFR, RAS can affect one or both kidneys, GFR depends on systemic blood pressure and ACE inhibitor dose, and other conditions can render GFR ACE inhibitor-sensitive.

A basic understanding of the mechanism of glomerular filtration allows us to interpret ACE inhibitor-induced changes in SCr, and to decide whether they warrant further investigation of the renal arteries or exclude the possibility of RAS.

KEYWORDS ACE inhibitors, renal function, renal artery stenosis

LIST OF ABBREVIATIONS Acute renal failure (ARF), angiotensin-converting enzyme (ACE), angiotensin receptor blockers (ARB), chronic kidney disease (CKD), glomerular filtration rate (GFR), renal artery stenosis (RAS), serum creatinine (SCr)

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CME

INTRODUCTION

It is common knowledge that ACE inhibitors can provoke ARF in patients with RAS. This inescapable fact obscures a complex series of clinical situations, including bilateral RAS, where renal function remains stable despite use of ACE inhibitors; and ACE inhibitor-induced ARF, where there is no RAS.

The effects of ACE inhibitors on renal function do, however, give substantial clues as to the existence or not of RAS. A basic understanding of how glomeruli filter, and why blood pressure and ACE inhibition affect this, is necessary to interpret the significance of ACE inhibitor effects on renal function.

Throughout this article, 'renal function' refers to renal excretory function as determined by GFR and as commonly measured by SCr. All ACE inhibitors are assumed to be identical in their effects on GFR, and it is highly likely that ARB have the same effects.

A LITTLE BIT OF RENAL HAEMODYNAMICS

Glomerular filtration rate is the difference between the flow of blood into the glomeruli via the afferent arterioles and the flow out via efferent arterioles. In normal circumstances this is not dependent on angiotensin II. However, kidneys have the capacity to increase GFR by local production of angiotensin II, causing vasoconstriction of the efferent arteriole. This increment of GFR is sensitive to ACE inhibitor, which prevent local angiotensin II generation. Glomerular filtration rate is commonly angiotensin II-dependent (and consequently ACE inhibitor-sensitive) when renal blood flow, and therefore afferent arteriolar flow, is reduced for whatever reason.

RENAL ARTERY STENOSIS, BLOOD PRESSURE, ACE INHIBITOR, AND GLOMERULAR FILTRATION RATE

In RAS, GFR becomes proportional to systemic blood pressure. In untreated hypertensive patients with bilateral RAS, GFR can be well maintained and the SCr remains near normal. The use of ACE inhibitors removes the partially protective effect of intrarenal Angiotensin II-mediated efferent arteriolar vasoconstriction. For a given blood pressure, the GFR will be less when ACE inhibitors are used. The blood pressure below which GFR will be virtually nil will be higher in the presence of ACE inhibitors. However, the three factors that affect GFR (ACE inhibitors, RAS, and systemic blood pressure) are all continuous variables. This needs to be taken into account when assessing a clinical situation, as discussed further below.

TWO CONFOUNDERS

Renal artery stenosis is not the only, or even the most common, cause of reduced renal blood flow. In any low blood pressure state (usually associated with hypovolaemia or low cardiac output), GFR becomes angiotensin II-dependent and therefore ACE inhibitor-sensitive. These states are usually easy to distinguish from RAS which is almost invariably associated with high blood pressure. Angiotensin-converting enzyme inhibitor-sensitive GFR is occasionally found in hypertension with no renal artery stenosis: these patients presumably have widespread hypertensive damage to small calibre intrarenal arteries and arterioles, limiting blood flow to the glomeruli.

In CKD of any cause, significant nephron loss, and therefore a drop in GFR, triggers a compensatory rise in GFR in the surviving nephrons. This is mediated via angiotensin II-induced efferent arteriolar vasoconstriction and is therefore ACE inhibitor-sensitive. The increment in GFR does not normally exceed 30%; so a fall in GFR (or rise in SCr) of up to 30% in cases of CKD is not unsurprising, and is not an indication for renal artery imaging. (Indeed, it is a sign of likely future benefit from the use of ACE inhibitors!)

CLINICAL SCENARIOS

An ACE inhibitor-induced rise in SCr of >30% in a patient with high blood pressure is always suspicious of RAS, especially in the presence of any clinically evident non-renal arterial disease. Bilateral RAS predisposes to episodic catastrophic pulmonary oedema. This is often misdiagnosed as left ventricular failure until the introduction of ACE inhibitors causes a rapid rise in SCr >30%.

Renal artery stenosis is particularly likely if the rise in SCr occurred in the absence of a significant drop in blood pressure. (In the face of low blood pressure, GFR is always angiotensin II-dependent/ACE-sensitive so there is no need to postulate RAS as well.)

It is certainly possible to introduce low-dose ACE inhibitors in hypertensive patients without significant change in SCr in the presence of bilateral RAS, especially if their blood pressure remains elevated. However, an unchanged SCr with therapeutic dose ACE inhibitor and controlled blood pressure virtually rules out bilateral RAS (or RAS in a single kidney). Because SCr only rises out of the normal range when GFR falls below about 50%, lack of change in normal SCr can tell us nothing about the possibility of RAS in one kidney if the other kidney is working well. It is not clear if this is an important diagnosis to make (or miss): the multicentre ASTRAL trial of intervention in RAS may help answer that question.

Angiotensin-converting enzyme inhibitor use is logical in the not infrequent scenario of a small kidney with little function beyond a very tight RAS or even renal artery occlusion, when the contralateral kidney has good function and no RAS. There is likely to be a renin-driven component to blood pressure arising from the ischaemic kidney, and switching off residual function in that kidney will produce only a trivial decrease in total GFR.

KEYPOINTS

- In renal artery stenosis, GFR becomes sensitive to blood pressure and ACE inhibitors. Understanding that the clinical variables are not absolute is vital to interpreting the significance of changes in SCr.
- Glomerular filtration rate is usually ACE inhibitor sensitive in the presence of hypotension or hypovolaemia: there is no need to invoke RAS as the cause.
- Glomerular filtration rate is ACE inhibitor sensitive in most cases of CKD, and decrements of <30% should not lead to a search for RAS.
- A rise in SCr >30% after ACE inhibitor, especially if blood pressure is maintained, is suggestive, but not diagnostic, of RAS.
- Stable SCr after normalisation of blood pressure with therapeutic doses of ACE inhibitor makes bilateral RAS very unlikely.

FURTHER READING

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