Where do we stand with renovascular hypertension?

Theresa Claus, Roland Schmitt, Christine Stabroth, Friedrich C. Luft, Ralph Kettritz and C. Michael Gross

Medical Faculty of the Charité, Franz Volhard Clinic, HELIOS Klinikum-Berlin, Germany

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In a bygone era, secondary hypertension was an easy issue. We had the obligation to investigate all hypertensive patients for secondary causes [1]. Patients identified with secondary hypertension were referred to an appropriate surgeon and the deed was done. After all, back then ‘a chance to cut was a chance to cure’. However, these pastoral times are gone, with the single exception of pheochromocytoma. Evidence-based medicine has chased us away from this lofty goal and we have become slaves to the Cochrane reports and ‘nothing is proved’. Whether or not this attitude is clinically acceptable in any given patient is a debate that clinicians face every day.

Case

A 46-year-old woman was referred because of decreased renal function and hypertension. She had developed nausea and vomiting and her physician observed a serum creatinine of 313 μmol/l. Fourteen years earlier, her left kidney was removed because of an adenoma that was suspected to be malignant but proved to be benign. Hypertension had been observed for several years. Her creatinine had been 70 μmol/l 10 years earlier but had increased to 88 μmol/l in 2002 and 92 μmol/l in 2003. Several months before admission, the value was 125 μmol/l. Her physician had treated her with an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin (Ang) II receptor (AT1) blocker. On physical examination, her blood pressure was 140/90 mmHg; however, with upright posture, both values decreased >10 mmHg. Funduscopic examination revealed arteriolar narrowing. Her cardiac point of maximum impulse was prominent. No abdominal bruit was observed. There were no other pertinent findings.

Her serum Na concentration was 120, Cl 86 and K 3.26 (all mmol/l). She had received a diuretic that day, so we did not measure the fractional Na excretion. However, the fractional urea excretion was 28%. We stopped all medication and gently infused normal saline. Her nausea and vomiting abated and in several days her Na increased to 140, the Cl to 99 and the K to 4.27 (mmol/l). The creatinine decreased to 133 μmol/l. There was no evidence of pheochromocytoma. We do not routinely measure renin and aldosterone in patients who are not hypokalaemic and therefore the values are not available. The kidney was normal in size by ultrasound. The electrocardiogram and echocardiogram were normal. We reinstituted the diuretic and the AT1 receptor blocker. Her creatinine promptly increased and her fractional urea excretion decreased to 18%, indicating pre-renal azotaemia [2]. The medications were discontinued.

Questions

1. What do the current results suggest and what tests should be performed?
2. Does ‘evidence-based medicine’ warrant any more tests?

We elected to perform duplex Doppler examination of the renal artery and then magnetic resonance imaging (MRI) angiography. Both tests raised the possibility of renovascular hypertension, but were not completely convincing. Digital subtraction angiography was then performed (Figure 1). Had we been aware of a recent report, we would probably not have
bothered the patient with the MRI angiogram [3]. We found that >150 reports on solitary kidneys and renal artery stenosis have been published. However, we were particularly impressed by the report first emphasizing the role of Ang II in maintaining the glomerular filtration rate via efferent arteriolar tone [4].

Questions

1. Is a prophylaxis for contrast-induced nephropathy warranted in this patient and, if so, which agent(s) should be given?
2. Can we tell whether or not the finding in Figure 1 means anything?

We gave both sodium bicarbonate and N-acetyl cysteine on the basis of a recent trial regarding the former and a meta-analysis regarding the latter, although we admit that both warrant further study. The available information suggests that prophylaxis should not be confined to diabetic patients [5,6].

We interpreted the finding as indicating the presence of fibromuscular hyperplasia in a solitary kidney based on the roentgenographic beaded appearance of the lesion. We then measured the resistance index with Doppler ultrasound and obtained a value of 78, barely <80 [7]. We next measured the gradient across the stenosis directly, before (Figure 2) and after (Figure 3) intra-arterial nitroglycerin. Before local nitroglycerin, the systolic gradient was 40 mmHg. After nitroglycerin, the pressures in the aorta were 157/110 mmHg (mean pressure 110 mmHg), while across the stenosis, the values were 78/57 mmHg (mean pressure 66 mmHg). The systolic gradient was 70 mmHg. We interpreted the values as justifying a percutaneous intervention according to our own data and those of others [8,9]. A stent was placed across the stenosis (Figure 4). Her creatinine decreased to 101 μmol/l by discharge and her blood pressure normalized without antihypertensive medications. She was instructed to take clopidogrel to maintain patency of her stent.

We are not aware of randomized double-blind studies on renal artery stenosis for fibromuscular hyperplasia. Randomized controlled trials are available for angioplasty treatment in patients with atherosclerotic renal artery stenosis. Plouin et al. randomized 26 patients to a control group and 23 patients to an intervention group [10]. Seventeen of the angioplasty patients had to have their medicines resumed. No impressive differences were observed. The authors concluded that non-blinded assessments of angioplasty overestimate the procedure’s potential for lowering blood pressure. The Dutch Renal Artery Stenosis Cooperative Study Group randomized 106 patients to control or angioplasty intervention [11]. The Dutch

![Fig. 1. Angiogram showing fibromuscular hyperplasia (string-of-beads) in a renal artery supplying a solitary kidney.](image1)

![Fig. 2. Simultaneous electrocardiogram and pressure recordings in the aorta and renal artery are shown. Note the pressure gradient.](image2)
group concluded that angioplasty had little advantage over antihypertensive drug treatment. The study has major problems including the fact that numerous patients were ‘crossed-over’ to angioplasty that had initially been assigned solely to drug treatment. The study was analysed per ‘intention to treat’. Thus, many physicians ‘already knew the answer’ and selected angioplasty for their patients. Neither of these studies can address the effect on reduced renal function to any satisfactory degree. For instance, the Dutch investigators included only those patients with creatinine values <200 μmol/l. A trial in the USA has begun to study all the issues again.

How do we justify our clinical decisions in this patient with so little ‘evidence-based’ information at hand? We screen those patients referred to us who are clinically remarkable. Decreasing renal function in the face of AT1 receptor or ACE inhibitor treatment is clearly an important clinical clue. Patients

Fig. 3. The pressure gradient was markedly increased with intra-arterial injection of 0.2 mg of nitroglycerin. This manoeuvre shows that the renal vasculature is capable of dilatation.

Fig. 4. The result after stent placement was gratifying.
with ‘flash’ pulmonary oedema, patients who cannot be controlled on >3 different classes of medications, patients with diastolic blood pressure values >125 mmHg, patients with severe atherosclerosis in the peripheral arteries, carotid arteries or coronary arteries are candidates for closer scrutiny. The father of modern renal physiology, a basic scientist and non-physician, Homer Smith, wrote one clinical article. The paper was about renal hypertension, and in the paper Smith observed that the prevalence of the condition varies with the population [12]. Amen to that.

Finally, how can we justify intervening in this patient and other patients without the necessary evidence? A recent report on the use of parachutes to prevent death and major injury after jumping out of airplanes emphasized the fact that the parachute has never been subjected to a randomized controlled trial, even though numerous reports of survival after jumping without a parachute have been published [13]. The authors recommended that ‘evidence-based’ fanatics be enrolled in such a trial. Surely, on the basis of the evidence, they could hardly refuse!

Teaching points

1. Increase in creatinine after ACE inhibitor or AT1 receptor blocker still suggests renal artery stenosis, classically in patients with a solitary kidney.
2. The work-up still ultimately relies on angiography.
3. Since we do not know that patients with two kidneys and renal artery stenosis benefit from treatment, large-scale screening or ‘drive by’ stenting are not indicated. Instead, we must carefully select those patients who are likely to profit from an intervention.
4. Finally, all nephrologists should know who Homer W. Smith was. Furthermore, all nephrologists should read the only clinical paper published by this giant in the field.

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References


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