Hibernating kidney on bilateral renal artery stenosis – the relevance of a costly diagnosis

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# Equal contribution

Abstract

We present the case of an elderly hypertensive, diabetic male patient with a ten-year history of chronic kidney disease and bilateral moderate atherosclerotic renal artery disease. During follow-up, the nephrologist observes a rapid worsening of kidney function and refers the patient to our clinic. Angiography describes severe (70–80%) bilateral renal artery stenosis and, in the setting of refractory hypertension confirmed by automatic 24hour blood pressure measurement and recent rapid progression of renal dysfunction, a decision for bilateral angioplasty with stent placement is taken. On follow-up, renal dysfunction is partially reversed, and blood pressure levels drop closer to target. Further, we discuss the rationale for interventional therapy in atherosclerotic renal artery disease and underline the key element in such a case – appropriate patient identification to select probable responders to treatment.

Introduction

The renovascular disease comes in two forms – fibromuscular dysplasia and atherosclerotic renal artery stenosis (RAS), the latter being more common, especially in older patients. Atherosclerotic RAS is found primarily in those with a high cardiovascular burden but may be the primary cause of hypertension in up to 10% of cases [1]. It is usually a major component of the pathophysiological pathway in previously diagnosed hypertensives, leading to resistant hypertension.

Atherosclerotic RAS is more often a result of concurring cardiovascular risk factors that lead to significant atherosclerosis in many vascular beds. It co-exists without clinical significance, except for a few severe presentations with hard-to-treat hypertension, flash pulmonary edema, congestive heart failure, or progressive renal failure [2]. Ferm

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indications to revascularize RAS have been the subject of controversy for decades. The three major trials addressing the topic, with their latter discussed limitations, included a wide range of patients with mild to moderate stenoses, thus leaving out specific "critical" subgroups in which clinical severity dictates interventional therapy in everyday practice [3–5]. Therefore, their negative results cannot be informative for decisions in such specific populations.

Here we present the case of a hypertensive male patient with bilateral atherosclerotic RAS and progressive renal failure in whom bilateral renal artery angioplasty with stent placement resulted in improved renal function and blood pressure control.

Case presentation

A 73-year-old Caucasian male, a non-smoker, was referred to our clinic due to the recent progression of renal dysfunction and uncontrolled blood pressure. His medical history in the past decade was relevant for dyslipidemia, type 2 diabetes mellitus, heart failure with preserved ejection fraction and had been followed-up by the referring nephrologist for the past ten years for stage three chronic renal disease in the setting of arterial hypertension and bilateral atherosclerotic renal artery disease evaluated by duplex sonography with a 50–60% stenosis. He had no history of stroke, myocardial infarction, or hypertensive emergency. Daily medical therapy consisted of a single pill combination of valsartan 160 mg, amlodipine 10 mg, nebivolol 10 mg, furosemide 40 mg, rilmenidine 2 mg, doxazosin 4 mg, atorvastatin 40 mg, and aspirin 75 mg. Insulin therapy was initiated one month prior due to worsening of the renal function, with a drop in the estimated glomerular filtration rate (eGFR) by the CKD-EPI equation from 48 ml/min/1.73 m^2 to 15 ml/min/1.73 m^2 (an increase in serum creatinine from 1.78 to 4.1 mg/dl).

Upon clinical examination, the patient was afebrile, in no apparent distress, with a body mass index of 29 kg/m^2, an abdominal circumference of 107 cm, heart rate of 60 bpm, blood pressure of 186/97 mmHg without significant difference between arms, and intense bruit over the lower abdominal quadrants. There were no signs of jugular venous hypertension, and auscultation of lung and heart sounds was normal. Peripheral pulses were diminished but palpable, and discrete malleolar edema was observed.

Laboratory testing revealed normal hemoglobin levels, total serum cholesterol – 165 mg/dL, LDL cholesterol – 99 mg/dL, triglycerides – 311 mg/dL, creatinine – 3.78 mg/dL (334.15 µmol/L), fasting serum glucose – 213 mg/dl (11.82 mmol/l) and glycated hemoglobin – 7.9%, serum uric acid – 11 mg/dL, normal serum sodium, potassium levels, normal serum thyroid hormone levels, and an increased NTproBNP at 1286 pg/mL. At the time, the albumin to creatinine ratio was 176 mg/g on two spot urine tests. Inflammation tests – erythrocyte sedimentation rate, serum fibrinogen, and C reactive protein – were within the normal range.

Electrocardiogram showed normal sinus rhythm, Sokolow Lyon voltage criteria for left ventricle hypertrophy, and secondary ST changes.

Automatic 24-hour blood pressure measurement revealed an average of 173/97 mmHg, with a riser dipping pattern having an awake-time average of 170/90 mmHg and an asleep-time average of 176/105 mmHg, with elevated pulse pressure and large systolic blood pressure variation.

Transthoracic echocardiogram was relevant for moderate concentric left ventricle hypertrophy with a mass index of 133.5 g/m^2 and normal ejection fraction, mildly dilated left atrium, and grade 2 diastolic dysfunction with high filling pressures.

Renal ultrasound was descriptive for small-sized kidneys – 8.7/4.3 cm on the right and 8/4 cm on the left, with elevated resistive indices on both sides at 0.75 on the right and 0.84 on the left. Duplex ultrasound revealed diffuse extensive calcified atheroma of carotid arteries without hemodynamic compromise.

Renal angiography was performed after careful risk-benefit ratio evaluation in a multidisciplinary team. On the left kidney, it revealed 80% stenosis in the proximal segment of the renal artery with diffuse, up to 70–80% stenoses of the secondary and tertiary arteries. At the time, angioplasty with stent placement was decided (Figures 1 and 2). On the right, there was 70% proximal renal artery stenosis, and this was amended by angioplasty with stent placement two months later in order to reduce each procedure duration and contrast exposure (Figures 3 and 4). Hemodynamic measurements were not performed due to the presence of consecutive multiple stenoses.

Before angiography, tentative blood pressure control increased the doxazosin dosage at 8 mg/day; also, the atorvastatin dosage was increased to 80 mg/day, and insulin therapy was adjusted aiming for improved glycemic control. Dual antiplatelet therapy was maintained for 30 days after each stent placement and was afterward switched to single antiplatelet therapy – clopidogrel 75 mg/day.

As a result of the first angioplasty, renal function improved gradually over the course of the first 72h to an eGFR of 31 ml/min/1.73m^2, with an additional further discrete gain in function to 35 ml/min/1.73 m^2 after the second intervention. Automatic 24-hour blood pressure measurement confirmed better blood pressure control at a 24-hour average of 145/83 mmHg.

Four months later, the patient presented with *de novo* angina, with no troponin release, electrocardiographic or cardiac echo changes, and angiogram

Figure 1. Left renal artery with 70–80% stenosis of the main artery, followed by multiple stenosis of intra-renal branches.

detected diffuse calcified coronary artery disease, with no blockage or significant stenoses. Renal function was stable, there was no renal artery restenosis, and he was started on extended-release isosorbide mononitrate for symptom control.

Discussion

The renovascular disease diagnosis is generally considered in the presence of certain clinical clues pointing towards either fibromuscular dysplasia (usually presenting as severe hypertension in young females, with unilateral small kidney, possibly affecting other vascular beds, in the absence of cardiovascular risk factors) [6, 7] or atherosclerotic renal artery stenosis. The presence of an abdominal bruit in a hypertensive patient, a discrepancy in kidney size or unexplained renal failure, new azotemia or significant worsening of renal function after initiation of renin-angiotensin-aldosterone system (RAAS) blockers, resistant or malignant hypertension [8] are clinical scenarios in which non-invasive imaging techniques, such as duplex ultrasound of renal arteries, computer tomography or magnetic resonance angiography can be performed, without overlooking their limitations

Figure 2. Left renal artery after successful balloon angioplasty and stent placement.
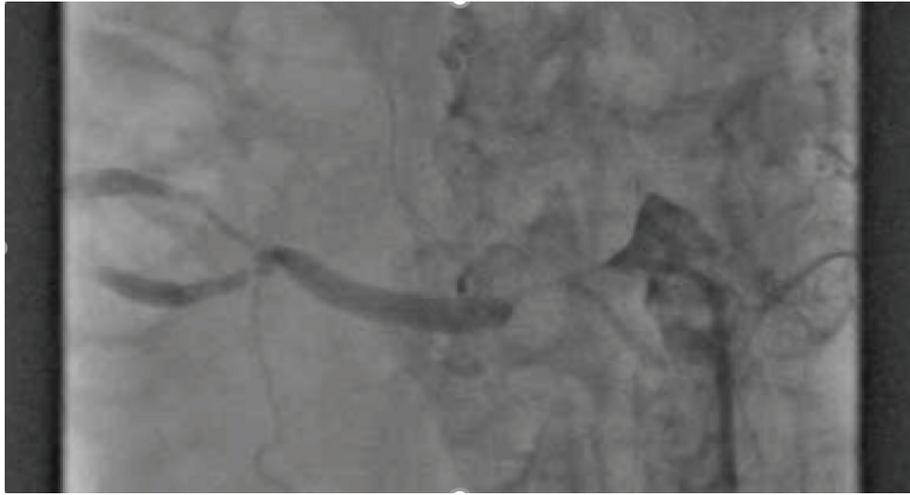
Figure 3. Right renal artery with 70% stenosis of the main artery.

and high probability to over-estimate stenosis severity [9]. More recently, blood oxygen level-dependent (BOLD) magnetic resonance imaging (MRI) has emerged as a novel non-invasive imaging technique able to objectify renal cortical hypoxia in patients with severe renal artery stenosis, thus enabling a risk-free diagnosis in such patients [10]. The gold standard for RAS diagnosis remains digital extraction angiography, but this is an invasive procedure, and the decision to employ it always takes into consideration the actual necessity to perform it, usually for revascularization purposes, which has met significant skepticism in the recent decade because of ever more evidence generally pointing towards no proof of benefit to improve blood pressure, renal or cardiovascular outcomes in recent trials.

Indeed, the most recent guidelines recommend against routine revascularization in atherosclerotic RAS [11, 12]. This decision was informed by the three randomized controlled trials (RCTs) performed to assess benefit on major cardiac outcomes of angioplasty for RAS during the recent past decades – CORAL [3], ASTRAL [4] and STAR [5]. The trials had their share of limitations: included relatively small numbers of patients, who did not necessarily meet criteria for resistant hypertension or were not optimized on antihypertensive therapy before interventions, the inclusion criteria allowed a wide range of moderate to severe RAS (≥50% in STAR, ≥60% in CORAL), eventually proving to have rolled-in mostly moderate stenosis in CORAL, where the investigator laboratory frequently over-estimated the degree of stenosis when compared to the central laboratory (core 67.3% vs. central 72.5%) [13]. This latter trial excluded those with congestive heart failure during the previous 30 days before enrollment [14]. Such details are relevant as they conclude that RAS angioplasty enters a grey area of medical indications, with only strict specific clinical scenarios in which revascularization is warranted, and that RCTs may prove yet unachievable in such subgroups due to low enrollment.

Figure 4. Right renal artery after successful balloon angioplasty and stent placement.

A few years after the above-mentioned trials were published, expert opinion revised diagnostic criteria for the invasive estimation of stenosis severity [15]. Consequently, they classified as significant either an angiographic stenosis severity over 70% or those with angiographic stenosis of 50–70% and invasively proven hemodynamic compromise of kidney circulation.

While angiography has evolved into a test carried out when interventional therapy is firmly considered, the quintessence of RAS management has thus become the identification of those likely to benefit from interventional therapy. Thereupon, the KDIGO Controversies Conference debates on atherosclerotic renovascular disease summarized the few indications currently recommended by expert opinion, settling the clinical scenarios likely to benefit from angioplasty in atherosclerotic RAS [14]. According to these recommendations, patient selection should consider the presence of either severe >75% stenosis or radiologic proof of hemodynamic compromise, some evidence of tissue viability – the "hibernating" kidney with nephropathy but some degree of reversibility, and the accompanying clinical syndrome. In a comprehensive review, Prince *et al.* outline the three major clinical syndromes of renal hypoperfusion: refractory hypertension, as defined in current guidelines [16], dynamic renal dysfunction with no other apparent cause, and cardiac destabilization syndromes [17]. In such cases, either interventional or surgical revascularization should be considered. In the absence of such criteria, most cases of RAS are similar to those included in the three major trials and have, therefore, strong evidence of the lack of benefit from interventional therapy, while best management focuses on optimizing pharmacological therapy and lifestyle. The aim is to ensure slower progression of atherosclerotic lesions, in the concern that unilateral or solitary RAS usually progresses, leading to loss of renal mass and impaired renal function evolving to stages where disease-modifying drugs such as RAAS blockers or mineralocorticoid antagonists (MRAs) cannot be continued. Progression to end-stage renal disease is rarely encountered in unilateral RAS but more likely in those with solitary or bilateral RAS [18, 19].

The patient presented had a long-standing history of bilateral moderate atherosclerotic renal artery stenosis in the setting of multiple cardiovascular risk factors. As the chronic kidney disease rapidly progressed over the course of weeks and blood pressure control was lost, our multidisciplinary team considered documentation of highly probable progression of bilateral RAS with the intention to restore kidney hemodynamics, delay progression to end-stage renal disease, improve blood pressure control and, consequently, the overall cardiovascular risk for major events. Even though current KDIGO guidelines recommend aggressive targets for systolic pressures under 120 mmHg [20], they were aimed, but not attained, by interventional therapy on top of the extended six-line antihypertensive therapy.

Continous RAAS blockade in such patients is recommended by current guidelines unless there is a rise by more than a third in serum creatinine levels within four weeks from dosage change [20], a statement expecting additional support from the currently ongoing STOP ACEi RCT trial [21]. Current practice is known to the usual "GFR dip" seen with initiation or escalation of RAAS blockers and MRA and is informed to rather evaluate therapeutic success with surrogates for renal function such as microalbuminuria [22].

In the absence of a severely reduced renal function, our diabetic, hypertensive, heart failure patient may have benefited from pharmacological therapies that have recently received hard evidence for improving blood pressure control (sacubitril-valsartan [23], sodium-glucose transport protein 2 inhibitors [24], and cardiovascular and renal morbimortality – sodium-glucose transport protein 2 [25]).

Recently, finerenone, a nonsteroidal selective MRA, was tested in the double-blind Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes (FIDELIO-DKD) trial [26]. Finerenone lowered the risk of chronic kidney disease progression and cardiovascular events in proteinuric patients with an eGFR of 25 to 60 ml/min/1.73 m², without excessive adverse events, making it an excellent alternative to currently available MRAs in such patients.

Conclusion

We present the case of an elderly hypertensive diabetic male patient with heart failure and preserved ejection fraction in whom recent worsening of renal failure with accompanying lack of blood pressure control mandated interventional therapy on top of the best pharmacological care. Timely intervention with flow restoration to a "hibernating" viable renal parenchyma led to improvement of renal function. In conclusion, the risk-to-benefit ratio inclines towards revascularization in specific high-risk populations. Thus, the focus in atherosclerotic renal vascular disease remains on the selection of responders to interventional therapy. Definite angiographic diagnosis is warranted when interventional therapy is firmly considered.

Conflict of Interest

The authors confirm that there are no conflicts of interest.

Acknowledgements

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