The Never-Ending Story of Complicated Hypertension

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Abstract
Polyvascular disease affects up to 20% of atherosclerotic patients and portends a significantly higher cardiovascular risk, especially in terms of ischemic events. Therapeutic options mainly focus on aggressive pharmacotherapy and risk factor control. We present the case of a male obese patient with coronary artery disease, chronic renal disease, and refractory hypertension who underwent serial contrast imaging to document the extent and severity of his systemic atherosclerosis and was consequently referred for cardiovascular surgery to address total occlusion of the abdominal aorta. We further discuss specific features complicating the medical management of patients with severe hypertension, extensive atherosclerosis, and renal disease.

Keywords
resistant hypertension, polyvascular disease, chronic renal disease

Rezumat
Boala polivasculară afectează până la 20% dintre pacienții cu ateroscleroză și prezintă un risc cardiovascular semnificativ mai mare, mai ales în ceea ce privește evenimentele ischemice. Opțiunile terapeutice se concentrează în principal pe farmacoterapie agresivă și pe controlul factorilor de risc. Prezentăm cazul unui pacient obez de sex masculin cu boală coronariană, boală renală cronică și hipertensiune arterială refractară, care a fost evaluat prin metode imagistice multimodale pentru a documenta amploarea și severitatea aterosclerozei sistemice și, ulterior, a fost trimis pentru intervenție chirurgicală a ocluziei complete de aortă abdominală. Vom prezenta caracteristicile specifice care complică managementul medical al pacienților cu hipertensiune arterială severă, ateroscleroză extinsă și boală renală.

Cuvinte cheie
hipertensiune arteriala rezistenta, boala polivasculara, boala cronica de rinichi

Introduction

In the pandemic of cardiovascular risk factors, with the aging of the population worldwide and in the setting of current medical advances, clinical practices nowadays frequently encounter patients with severe diffuse cardiovascular disease whose diagnosis and management requires carefully balancing the risks and benefits of procedures undergone by our evermore fragile patients to ensure adequacy and safety.

After longstanding hypertension, diabetes, chronic renal disease, and diffuse atherosclerosis, specific patients with polyvascular disease become resistant to drug therapy, entering a vicious cycle of cardiovascular disease progression. In trials and registries, polyvascular disease was found to affect atherosclerotic patients in different percentages—from 10% to as high as 43% more recently [1] —and this data portends a significantly higher cardiovascular risk, especially in terms of ischemic events [2]. Therapeutic options mainly focus on aggressive pharmacotherapy and risk factor control. Such intervention is harder to employ in resistant hypertensives in whom the risk to recurrent vascular events and cardiovascular mortality is higher. To portray the complexity and frailty of such patients and the difficulty of managing their disease in clinical practice, we further present the case of a male obese patient, with coronary artery disease, chronic renal disease, and refractory hypertension who underwent serial contrast imaging to document the extent and severity of systemic atherosclerosis and was consequently referred for cardiovascular surgery to address total occlusion of the abdominal aorta. We further discuss specific features complicating the medical management of patients with severe hypertension, extensive atherosclerosis, and renal disease.

Case Presentation

We present the case of a 60-year-old patient admitted to our clinic with short-distance claudication (<100 meters) and uncontrolled blood pressure values. He also described dyspnea and reduced tolerance to moderate-high exertion that had developed over the course of the previous four months. His medical history painted the picture of a patient with severe polyvascular disease. When considering his cardiovascular risk factors, it's important to note that he was a heavy smoker (30 pack years), weaned during the previous 3 months, and suffered from severe hypertension and stage 4 chronic kidney

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disease. He was diabetic with adequate glycemic control through a healthy diet but was dyslipidemic and hyperuricemic. Ten years prior to the current presentation, he was diagnosed with ischemic coronary heart disease and exertional angina and underwent percutaneous coronary intervention with pharmacologically active stent implantation at the first marginal circumflex, leaving him angina free over the following years. Three years later, he suffered a minor stroke, with no neurological sequelae, and after another two years, the patient was diagnosed with complete occlusion of the left renal artery and thus underwent left nephrectomy. With the onset of claudication and dyspnea, he underwent an outpatient ultrasound evaluation which was diagnostic for an abdominal aortic sub-occlusion. He had been diagnosed with severe sleep apnea syndrome but did not tolerate home continuous positive airway pressure therapy.

At the time of presentation in our clinic, the patient was on six antihypertensive drugs: amlodipine 10 mg b.i.d., furosemide 40 mg o.d., carvedilol 6.25 mg b.i.d., clonidine 0.15 mg t.i.d., methyldopa 250 mg t.i.d., doxazosin 4 mg b.i.d. He was also receiving 100 mg of aspirin, 20 mg atorvastatin, 100 mg allopurinol. Being ever more sedentary since the intermittent claudication and reduced exercise tolerance overlapped, the patient had a less than optimal lifestyle.

At the time of admission, clinical examination revealed an obese male patient with a BMI of 34 kg/m2. Pulmonary examination was insignificant, with normal bilateral vesicular murmur, without rales or wheezes, and a peripheral oxygen saturation of 98% in room air with normal respiratory rate at 17 rpm. Cardiovascular examination revealed rhythmic heart sounds, without cardiac murmurs or bruits, without signs of systemic congestion, but with a significantly and persistently elevated blood pressure (equal between arms) at 180/90 mmHg. Arterial pulse was diminished at the femoral arteries, with no palpable peripheral pulse distally. Abdominal examination was also unsignificant, with no bruits. Diuresis was physiological at 1000-2000 mL/24h, without dysuria.

Laboratory studies showed the following: hemoglobin 12.1 g/dL with normal red blood cell indices and normal ferritin and serum iron levels; normal white blood count and platelets; normal liver function; total protein 6 mg/dL; albumin 3.9 mg/dL; normal serum sodium, potassium, and chloride levels; and a fasting glucose of 109 mg/dL with a glycated hemoglobin of 6.5%. Lipid profile was altered with a total cholesterol of 218 mg/dL, an LDL-cholesterol of 157 mg/dL, and high serum triglycerides at 170 mg/dL. Renal function was severely affected with high serum creatinine values ranging from 4.51 mg/dL on admission to a minimum of 3.41 mg/dL upon discharge—corresponding to a range of estimated glomerular filtration rates that position the renal dysfunction at the boundary between stage 4 and stage 5 chronic kidney disease. There was also relevant nephrotic range proteinuria at 9.6 g/24 h, a measurement carried out in the first days of admission when blood pressure levels were highly elevated. Admission NTproBNP values were increased at 2960 pg/mL, and TSH was 7.12 uUI/mL, which in the context of subclinical hypothyroidism did not justify initiation of hormone replacement therapy.

Upon admission, the chest X-ray revealed an increased cardiothoracic index, without signs of pulmonary congestion or pleural effusion (Figure 1).

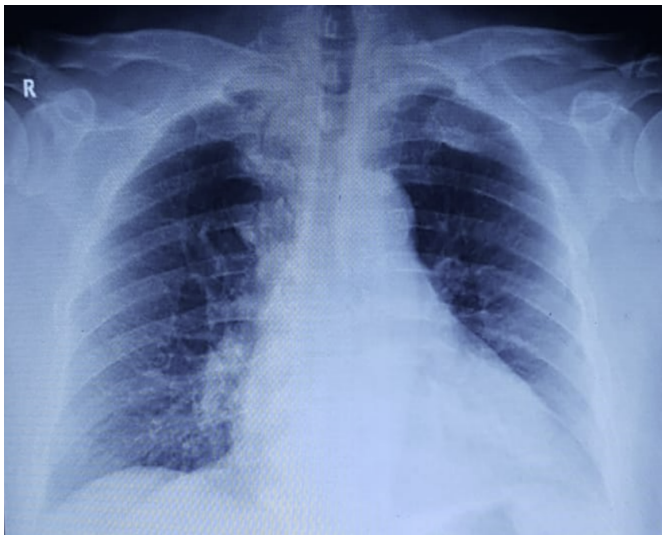


Figure 1 - Chest X-ray upon admission showing an increased cardiothoracic index, with no signs of pulmonary congestion or pleural effusion.

Electrocardiography shows bradycardic sinus rhythm at 45 bpm, a corrected QT by Bazett formula at 416 ms, Cornell criteria for left ventricle hypertrophy, and negative T waves in the lateral territory: DI, aVL, V5, V6 (Figure 2). Sinus bradycardia was persistent throughout the hospitalization and motivated the (later acknowledged as ineffective) withdrawal of both clonidine and the beta-blocker.

Echocardiography found a normal sized left ventricle with severe concentric hypertrophy and normal systolic function, but with subclinical longitudinal systolic dysfunction with reduced global longitudinal strain predominantly in the infero-lateral basal segments. There was grade 2 diastolic dysfunction with severe left atrium dilation, high left atrium filling pressures, but no significant valve disease. There were no elements suggestive of pulmonary hypertension or right heart disease (Figure 3).

To evaluate the extension of atherosclerosis, carotid Doppler ultrasound was carried out. It showed bilateral, small, calcified atheroma arranged discontinuously along the common carotid arteries, along the bifurcation, and extending within the internal carotid arteries, completing the picture of bilateral carotid atherosclerosis without hemodynamically significant stenoses.

Upon 24-hour monitoring we found a riser-type dipping pattern with an average blood pressure of 196/92 mmHg (Figure 4). Holter monitoring showed sinus rhythm with an average heart rate of 50 bpm and rare premature ventricular and supraventricular beats, with no pauses, rhythm, or conduction disorders.

Peripheral angiography described a thin looking abdominal aorta with significant parietal thrombosis and a 30–40% stenosis followed by complete occlusion immediately above the bifurcation at the level of the fourth lumbar vertebral body (Figure 5). The common femoral artery was bilaterally supplied by well-developed collaterals stemming from the first and forth lumbar arteries. The right renal artery had a 40% tubular stenosis in the proximal segment, with a homogeneously opaque (preserved) nephrogram. The left renal artery was not visible, as expected after nephrectomy. Angiography

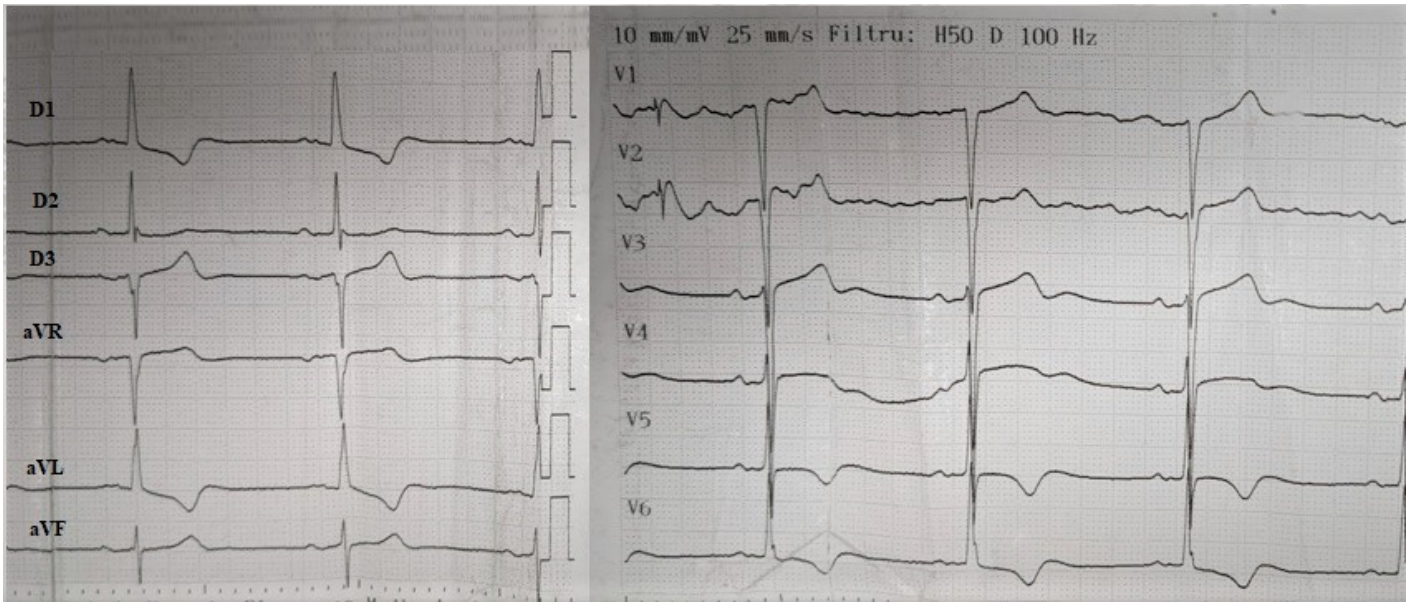


Figure 2 - Electrocardiogram upon admission showing bradycardic sinus rhythm at 45 bpm with a corrected QT by Bazett formula of 416 ms, with Cornell criteria for left ventricle hypertrophy, and negative T waves in the lateral territory – DI, aVL, V5, V6.

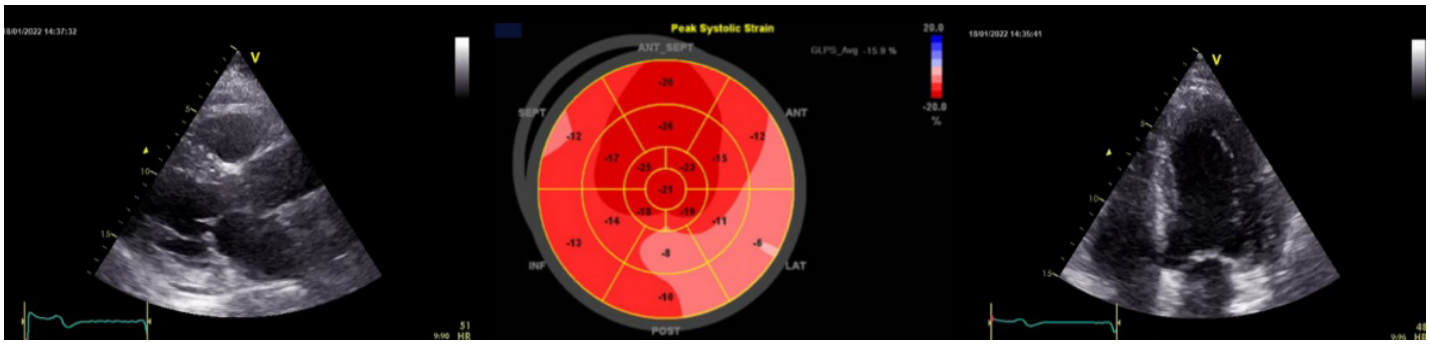


Figure 3 – Echocardiography with normal sized left ventricle but severe concentric hypertrophy and normal systolic function. Tissue Doppler Imaging revealed subclinical longitudinal systolic dysfunction with reduced global longitudinal strain predominantly in the infero-lateral basal segments.

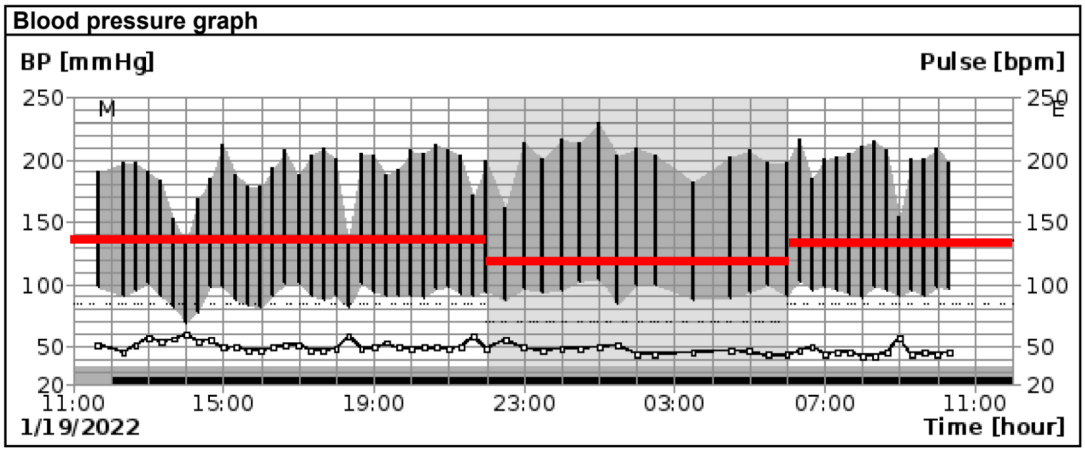
also diagnosed ostial sub-occlusion of the inferior mesenteric artery. The celiac trunk and the superior mesenteric artery were permeable. The femoral-popliteal axis was also bilaterally permeable, but with delayed flow distally.

To complete the extensive evaluation of vascular disease in relative safety in terms of the nephrotoxicity of contrast agents, a few days after the previous investigation we performed a coronary angiography which revealed a short, calcified left main without significant lesions. The left anterior descending artery was calcified, with extensive atherosclerotic infiltration, and a 20–30% stenosis of the proximal segment. The circumflex artery had extensive atherosclerosis without significant lesions and the previously implanted stent was permeable; the right coronary artery was calcified, with ostial chronic total occlusion, and retrograde supply from the left anterior descending artery (Figure 6).

The repeated imaging fortunately did not precipitate a sudden, acute deterioration of renal function.

Drug wise, in the hope for better pressure control, the loop diuretic was switched to torsemide as an option with better bioavailability and pharmacokinetics, and the antihypertensives with central and vasodilating effect were slowly up-titrated—methyldopa to 500 mg t.i.d. and doxazosin 8 mg b.i.d. By the time of discharge blood pressure control was marginally improved to an average systolic of 140–150 mmHg, and repeat proteinuria settled at 2.4 g/24h. There was an attempt to introduce an angiotensin converting enzyme inhibitor, but the rapid tendency to hyperkalemia and deteriorating renal function forbade it. Aspirin was kept and atorvastatin was increased to 80 mg o.d.

Eventually, the patient was referred to surgery for peripheral revascularization by aorto-bifemoral bypass, an intervention he preferred to postpone and reconsider.



SUCCESSFUL READINGS 95%	
Average 24h blood pressure	195/92 mmHg
Average awake blood pressure (systolic StDev)	193/92 mmHg (20 mmHg)
Average asleep blood pressure (systolic StDev)	202/94 mmHg (19 mmHg)
Dipping pattern	Riser (-3%)

Figure 4 - 24h Blood pressure monitoring displaying a riser-type dipping pattern and average blood pressure of 196/92 mmHg with high systolic variability.

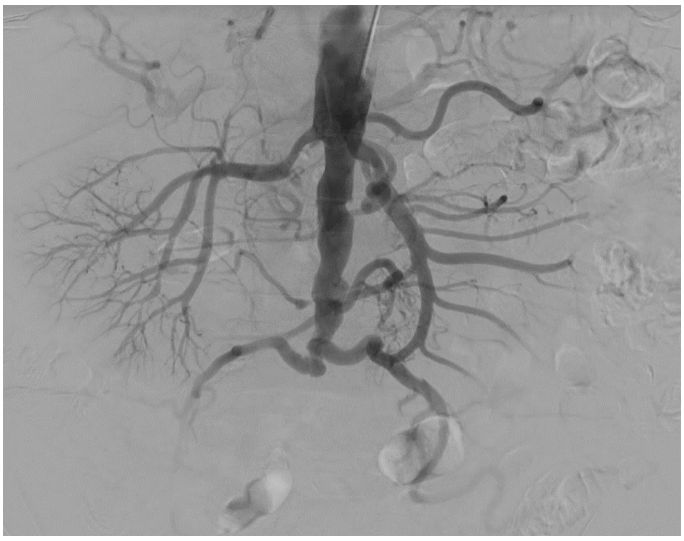


Figure 5 - Peripheral angiography showing right renal artery 40% tubular stenosis in the proximal segment, with a homogeneously opaque (preserved) nephrogram. Left renal artery is not visible after nephrectomy.

Discussion

Resistant hypertension is defined as uncontrolled blood pressure confirmed either by ambulatory or home blood pressure monitoring under at least three antihypertensive drugs of which one is a diuretic, in a patient in whom pseudo-resistance and secondary hypertension have been excluded [3]. When properly documented, less than ten percent of such patients are truly resistant [4]. While reversible causes for hypertension should be suspected in young patients, in the elderly they oftentimes accompany the clinical picture of primary hypertension and should be sought only in the presence of symptoms and signs suggestive for a specific pathology [3]. As such, the process of documenting resistant hypertension may lead to the discovery of reversible causes which, once acknowledged and addressed, may improve blood pressure control.

Resistant hypertensive patients usually have a particular profile of long-standing hypertension, obesity, diabetes, and, consequently, significant hypertension mediated organ damage such as left ventricular hypertrophy, albuminuria, or chronic renal disease [5]. Their co-occurrence may advocate for differential diagnosis with specific pathology sharing similar phenotypes and may prove sometimes difficult to discriminate with non-invasive procedures [6]. Moreover, the presence of polyvascular disease in a resistant hypertensive patient portends a worse prognosis, and as such, patients appear to undergo a second major cardiac event up to ten years earlier than controlled hypertensives [7].

A similar profile was evident in the patient presented above. Long standing arterial hypertension and diabetes mellitus, along with non-optimal control of cardiovascular risk factors and established severe polyvascular disease maintained the progression of renal disease and cardiovascular disease, thus further promoting lack of blood

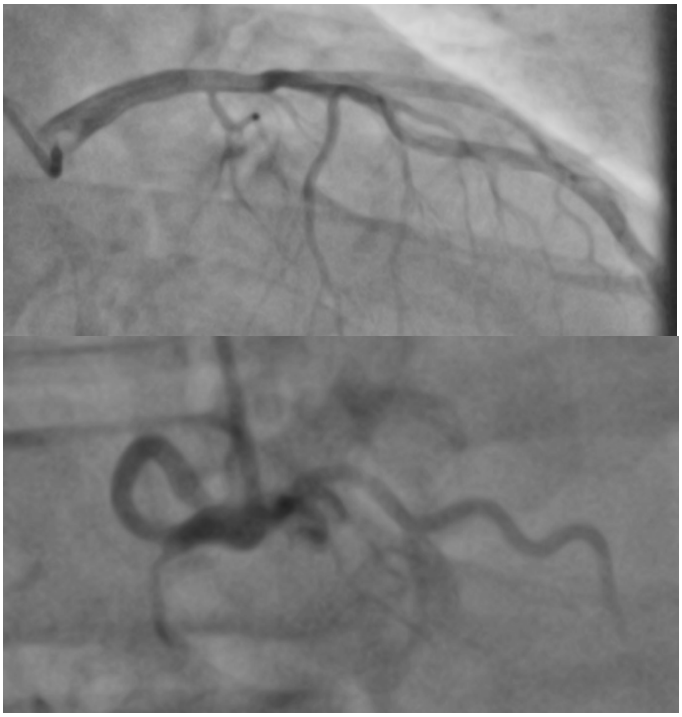


Figure 6 - Coronary angiography showing circumflex artery with extensive atherosclerosis without significant lesions permeable stent and calcified right coronary artery with ostial chronic total occlusion.

pressure control which exacerbates the risk of major events in a permanent, vicious cycle.

Our patient had been previously diagnosed with severe obstructive sleep apnea but did not tolerate continuous positive airway pressure therapy. There has been extensive literature discussing the pathophysiology of hypoxemia mediated sympathetic overdrive as a significant component to resistant hypertension [8,9]. And several trials have tested the efficacy of continuous positive airway pressure therapy to improve blood pressure control [10] more recently, proving a small but significant blood pressure lowering effect, independent of sympathetic stimulation [11]. However, a meta-analysis of such trials has found only minimal reductions in blood pressure, and there are no outcome data to support a long-term prognostic value [12]. Adherence to continuous positive airway pressure therapy may be an issue, as studies have found a 10 to 20% occurrence rate of non-compliance to such therapy, mostly driven by facial mask related side effects [13].

In our patient, angiography documented a 40% tubular stenosis in the proximal segment of the right renal artery. This finding may be misleading in a resistant hypertension patient, as such degree of stenosis does not entail significant alteration in renal hemodynamics and should not be viewed as a cause for resistance [14]. Here, long standing hypertension and diabetes have most probably promoted and sustained a chronic decline in renal function characterized by glomerulosclerosis and afferent and efferent hyaline arteriolosclerosis [15]. The more recent ischemic nephrectomy had further contributed to a net loss in glomerular filtration capacity. At this point, chronic kidney disease acted as both a consequence and a promoter of hypertension in a complex interplay fueling improper sodium handling leading to extracellular volume expansion, sympathetic hyperstimulation, and activation of the renin angiotensin aldosterone system [16]. In the last stages of renal disease, the pharmacological armamentarium available for blood pressure reduction and cardiovascular and renal protection is considerably limited, thus setting the course to an inexorable path to end stage disease. In our patient, the chronic evolution of atherosclerotic disease was highly suggestive to distinguish hypertensive and diabetic nephropathy from other types. In the context of severe left ventricular hypertrophy and nephrotic range proteinuria, however, a differential diagnosis with gammopathies may be considered. The echocardiography details described in our patient (the myocardial deformation pattern and the absence of signs of pulmonary hypertension) made cardiac amyloid as a promoter of hypertrophy highly improbable [17]. Such patients are usually hypotensive and are very sensitive to blood pressure lowering agents [18]. In the absence of hypoalbuminemia, edema, and signs of volume depletion, there was no clinical nephrotic syndrome [19]. The decrease in protein excretion parallel to the lowering of blood pressure values (and subsequently intraglomerular pressure) supported an argument for hypertensive nephrosclerosis as a main substrate for severe proteinuria [20]. Instead, it probably worsened the refractory nature of our patient's hypertension because it usually further aggravates glomerular damage and promotes chronic kidney disease progression, especially in the absence of antiproteinuric drugs such as angiotensin converting enzyme inhibitors or sartans.

Denying therapy to chronic renal disease patients was coined as renalism, in an attempt to address and amend the unjustified limitation to angiography in this patient population due to the fear of radiocontrast-associated nephrotoxicity [21]. In our polyvascular disease patient, the angiography procedures had a high diagnostic yield and settled the indication for surgery. The risk for contrast induced acute kidney injury is higher in those with severe diffuse atherosclerosis [22], but was limited (<5%) in the two largest trials. These trials have included over 5000 patients and tested *and* disproved the effectiveness of preventive strategies employing n-acetyhl cysteine or sodium bicarbonate versus saline after angiography [23]. A meta-analysis of 124 trials and 28,240 patients undergoing percutaneous coronary procedures, found that statin administration was the only effective preventive strategy, while xanthine, n-acetyl cysteine, sodium bicarbonate, or ischemic preconditioning did not show consistent results across studies [24]. Current clinical guidelines [25] recommend hydration to prevent contrast associated kidney injury. However, a recent trial found that a strategy with no hydration prophylaxis was non-inferior and cost-saving in this sense [26]. All these data reinforce the need for proper documentation of vascular disease in renal patients acknowledging the risks, but also aiming for their major benefits.

If surgery is being contemplated to improve symptoms, the informed decision should take into consideration that the Lee score

places our patient at a very high risk of post-operative cardiovascular complications such as myocardial infarction, cardiogenic pulmonary edema, cardiac arrest, or complete atrioventricular block [27]. Meanwhile, the NSQIP score does not place him at a very high risk, but it does not apply to patients with kidney failure [27]. This score however offers the opportunity to adjust the calculation when intuition informs the surgeon of a higher risk of unfavorable outcomes. This recalibrates the scale away from the safe zone in the case of our patient, and thus, in a comprehensive risk evaluation scenario, the risk for fatality in case of surgery is highly significant.

Conclusion

We presented the case of a polyvascular disease patient with chronic renal disease and refractory hypertension, with a firm indication for cardiovascular surgery for total occlusion of the abdominal aorta in the presence of sub-optimally controlled cardiovascular risk factors. This has become a profile frequently seen in clinical practice. Thus, a more aggressive approach to diagnosis and pharmacological therapy is mandated in order to improve both symptoms and long-term prognosis in such very high-risk patients. Unfortunately, in our case an optimal pressure control could not be obtained, with blood pressure values still in the 140–150 mmHg systolic range, far from guideline targets in chronic renal disease, proteinuric, hypertensive patients, therefore most likely accelerating a relentless evolution towards end stage and dialysis.

Conflict of interest

None to declare.

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