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Case Report
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Aortic stenosis and difficult to treat hypertension: an impossible duo?

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Abstract

An 84-year-old female patient was admitted to our clinic for progressive shortness of breath and low functional capacity for one month. She has been hypertensive for almost 30 years, currently with poor blood pressure control despite four antihypertensive drugs. There were no signs of systemic or pulmonary congestion, but a holosystolic murmur in the aortic area was present. The echocardiography revealed moderate concentric left ventricular hypertrophy and a global longitudinal strain of -14.1%, indicating subclinical longitudinal systolic dysfunction of the left ventricle but with preserved ejection fraction. The tricuspid aortic valve had important degenerative structural changes, with an indexed area of 0.55 cm2/m2 indicating severe stenosis. Abdominal contrast computed tomography revealed a small area of cortical hyperplasia in the left adrenal gland, along with calcifications of both renal arteries from their origin, resulting in 60% bilateral stenosis. The antihypertensive treatment did not provide sufficient control, with average overall values of 165/77 mmHg on 24h ambulatory blood pressure monitoring with a non-dipper pattern. Thus, a diagnosis of grade 3 stage 3 arterial hypertension was established in a patient recently diagnosed with severe degenerative aortic stenosis. We reckon that the cause of the inadequate blood pressure control included the combination of suboptimal treatment selection and titration, along with persistent causes of hypertension such as atherosclerotic renovascular disease, sleep apnoea and possibly primary hyperaldosteronism. The optimal treatment approach combined reinforcement of lifestyle measures with antihypertensive drugs, considering all medication classes, including blockers of the renin-angiotensin-aldosterone system, despite the presence of severe aortic stenosis.

Keywords: Aortic stenosis, arterial hypertension, hypertension treatment.

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Introduction

Aortic valve stenosis is the third most common cardiovascular disease, usually secondary to degeneration of a tricuspid valve in older patients, the preva-

lence increasing up to 10% in octogenarians [1, 2]. On the other side, arterial hypertension (HTN) was estimated to affect almost 1.13 billion people globally in 2015, and its prevalence also increases with age [3]. Thus, we are facing two common cardiovascular diseases with similar risk factors, which were surprisingly not very frequently linked in the past.

Low systolic blood pressure (BP) values have been considered hallmark signs of aortic valve stenosis due to fixed left ventricular outflow obstruction [4]. Nevertheless, a thorough review of the literature, dating back to almost twenty years ago, suggests that the association between aortic stenosis and arterial HTN is not rare. The prevalence of this association varies from 61% to 92%, and older women have the highest burden of hypertensive heart disease [5]. This becomes plausible if we consider that arterial hypertension is a risk factor for the development and progression of aortic valve stenosis and also that this valvular disease may cause systolic hypertension [3, 4].

The relationship between aortic stenosis and HTN can be defined through atherosclerosis. Aortic stenosis should not be viewed as an isolated valve disease but rather as a systemic atherosclerotic disease involving both the aortic valve and the systemic arteries. Also, atherosclerosis reduces the compliance of the systemic arteries leading to hypertension [7].

Case report

We present the case of an 84-year-old female patient who was admitted for progressive shortness of breath and low functional capacity for one month. The patient had multiple cardiovascular risk factors (dyslipidemia, obesity, age), including grade 3 arterial HTN. She has been hypertensive for almost 30 years with poor blood pressure control in the past year, reporting constantly elevated BP above 160/90 mmHg. Her current antihypertensive treatment regimen included valsartan 160 mg b.i.d, lercanidipine 10 mg o.d., metoprolol succinate 50 mg o.d. and methyldopa 250 mg q.i.d. Her past medical history also included two episodes of ischemic vertebrobasilar stroke, currently treated with antiplatelet therapy and lipid-lowering drugs, and a diagnosis of left bundle branch block (LBBB).

The **clinical examination** revealed a patient with grade I obesity (body mass index of 32.6 kg/m^2) and no signs of systemic or pulmonary congestion. The BP in the supine position was 160/80 mmHg, equal in both arms, without any significant dropping after one and three minutes of orthostatic position. The patient had a regular heart rate of 62 bpm. The cardiac auscultation revealed a holosystolic murmur grade 3/6 in the aortic area, radiating to the carotid arteries, and another one in the mitral area, radiating to the left axillary region. Peripheral pulse was present, with the classic sign parvus et tardus. The patient had limited physical capacity, being able to perform activities requiring 4 metabolic equivalents (METS).

The **laboratory** tests indicated stage G2 A3 renal dysfunction according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (eRFG 64 mL/min/1.73 m2) with a urinary albumin:creatinine ratio of 420 mg/g. NT-proBNP was increased, with a value of 1.670 pg/mL. The hemogram was within normal limits, as were the liver and thyroid function. The lipidic profile was not within the therapeutic target as LDL-cholesterol had a value of 60 mg/dL, total cholesterol 126 mg/dL and triglycerides 131 mg/dL. Mild hypokalaemia was also identified (3.83 mmoli/L).

Electrocardiogram (EKG) on admission showed sinus rhythm, with left axis deviation and known complete left bundle branch block with appropriate discordant repolarization changes (ST-segment depression and T wave inversion) in the lateral leads (Figure 1). During the hospital admission, routine EKG monitoring revealed approximately three minutes of paroxysmal atrial fibrillation.

The **chest X-ray** performed at the time of admission showed a calcified aortic knob but was otherwise unremarkable.

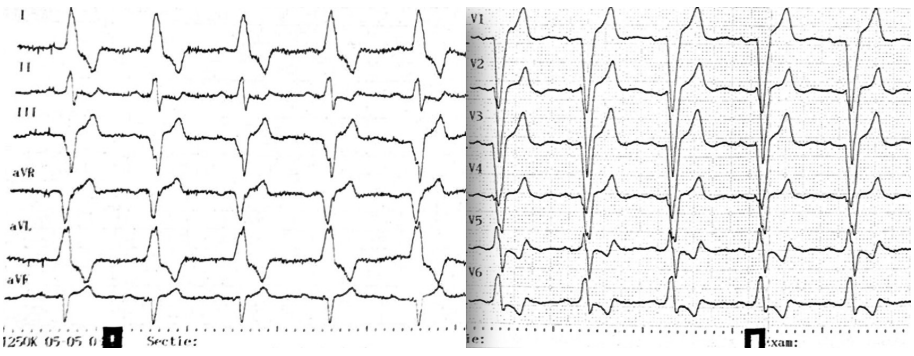

Figure 1. Electrocardiogram showing sinus rhythm, left axis deviation and complete left bundle branch block with secondary repolarization changes.

Echocardiography revealed moderate concentric left ventricular (LV) hypertrophy (LV mass index -LVMI- 135 g/m2, relative wall thickness -RWT- 0.48), as shown in Figure 2A. The global systolic function was normal as assessed with the biplane Simpson's method (LV ejection fraction 58%). However, the global longitudinal strain of -14.1% indicated a subclinical longitudinal LV systolic dysfunction (Figure 2B).

The aortic valve evaluation showed a tricuspid valve, with important degenerative structural changes that generated severe stenosis and mild to moderate regurgitation. The indexed aortic valve area (AVAi) calculated with the continuity equation method showed a value of 0.55 cm2/m2, as indicated in Figure 3. It is important to mention that the BP and heart rate were well-controlled when the examination was performed for a reliable assessment of the severity.

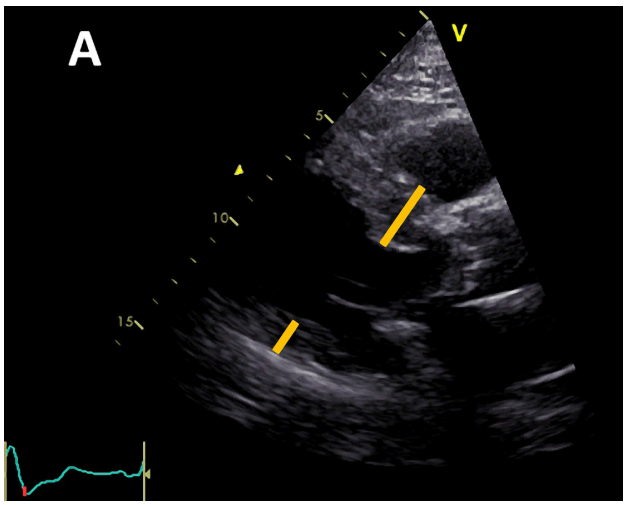

Figure 2A. Echocardiography - parasternal long axis view. Left ventricular (LV) hypertrophy without LV enlargement.

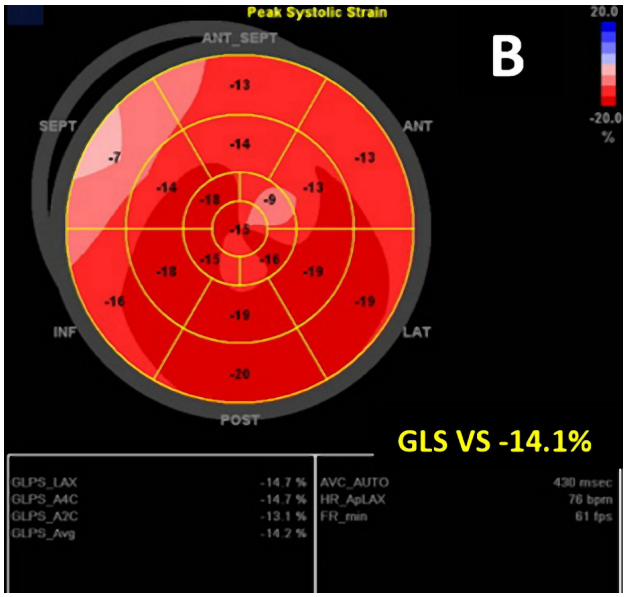

Figure 2B. "Bull's eye" display of left ventricle longitudinal strain – Global longitudinal strain (GLS) is reduced, indicating a mild systolic longitudinal dysfunction.

The left atrium was severely dilated (indexed volume of 49 mL/m2). The right ventricle had normal function and dimensions, and pulmonary hypertension was improbable.

In front of a patient with severe aortic stenosis, we aimed to confirm the difficult-to-control HTN using automated BP measurements (ABPM). On 24-hour ABPM, mean 24-hour BP was severely elevated - 165/77 mmHg. Mean diurnal BP was 169/79 mmHg, mean nocturnal BP was 155/72 mmHg with a non-dipper pattern (dipper index of 8%). Moreover, the pulse pressure (PP) weighted average was increased at a value of 88 mmHg.

Even though improbable, four antihypertensive drugs did not provide sufficient control, resulting in severe HTN in a patient with severe aortic stenosis. Therefore, we sought to investigate the possible causes of secondary HTN and to evaluate the degree of HTN-mediated organ damage (HMOD).

Abdominal echography indicated normal and equal renal dimensions, with a hypoechoic mass of 3.5/2.4 cm in the area of the right adrenal gland. Further investigations, which included abdominopelvic **computed tomography**, revealed two possible causes of resistant HTN. The structure of the right adrenal gland was normal, but a small area of cortical hyperplasia in the left adrenal gland was discovered. The kidneys had some cortical cysts of a maximum of 3 cm in diameter on the right side (Figure 4D), but the function was normal. However, calcifications of both renal arteries were present from their origin, leading to a 60% bilateral stenosis (Figure 4 C, D).

Moreover, a mild form of obstructive sleep apnoea (OSA) was diagnosed by polygraphy, with an apnea-hypopnea index of 14/h.

The complete evaluation of HMOD showed a pulse wave velocity (PWV) of 13 m/s and a PP weighted average of 88 mmHg, indicating aortic stiffness, despite a normal value of the ankle-brachial index (ABI = 0.98). However, the patient had established cardiovascular disease - diffuse atheromatous plaques without hemodynamic impairment on carotid ultrasound, a history of ischemic strokes, heart failure with preserved ejection fraction (HFPEF) and chronic kidney disease.

Taking into account two episodes of ischemic stroke in a patient with non-obstructive stable carotid plaques, we suspected a possible embolic stroke. We repeated the 24-hour Holter monitoring twice, and we were eventually able to demonstrate sustained episodes of paroxysmal atrial fibrillation.

A diagnosis of grade 3 stage 3 arterial hypertension was established in a patient recently diagnosed with severe degenerative aortic stenosis. We reckon

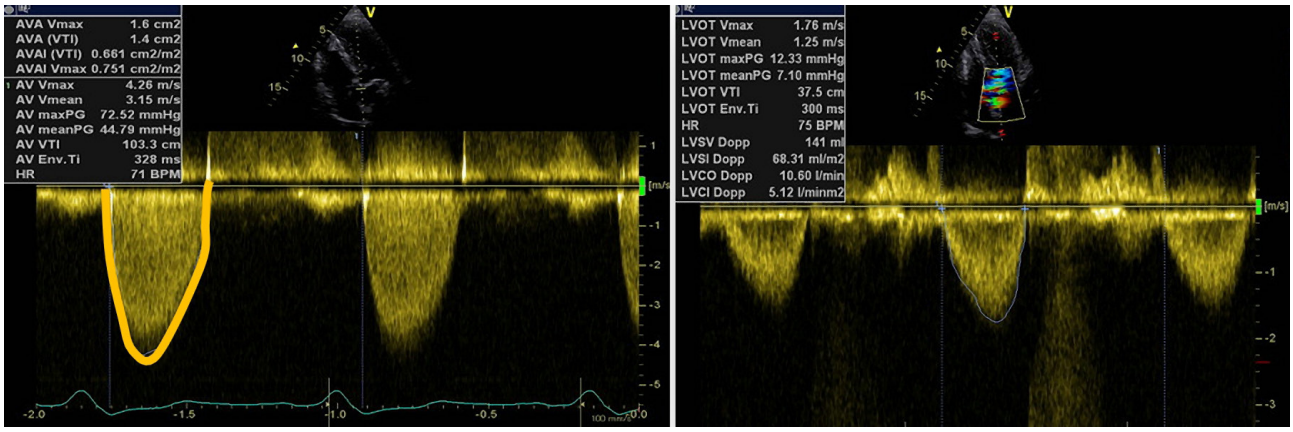

Figure 3. Echocardiography – continous and pulse wave Doppler tracings of the aortic valve interogation. Aortic valve area (AVA) calculation by continuity equation considering the following parameters – LVOT diameter (20 mm), LVOT VTI (37.5 cm) and Ao VTI (103.3 cm). The indexed AVA value is significant for severe aortic valve stenosis.
AoVTI - Aortic velocity time integral; LVOT VTI - Left ventricular outflow tract velocity time integral.

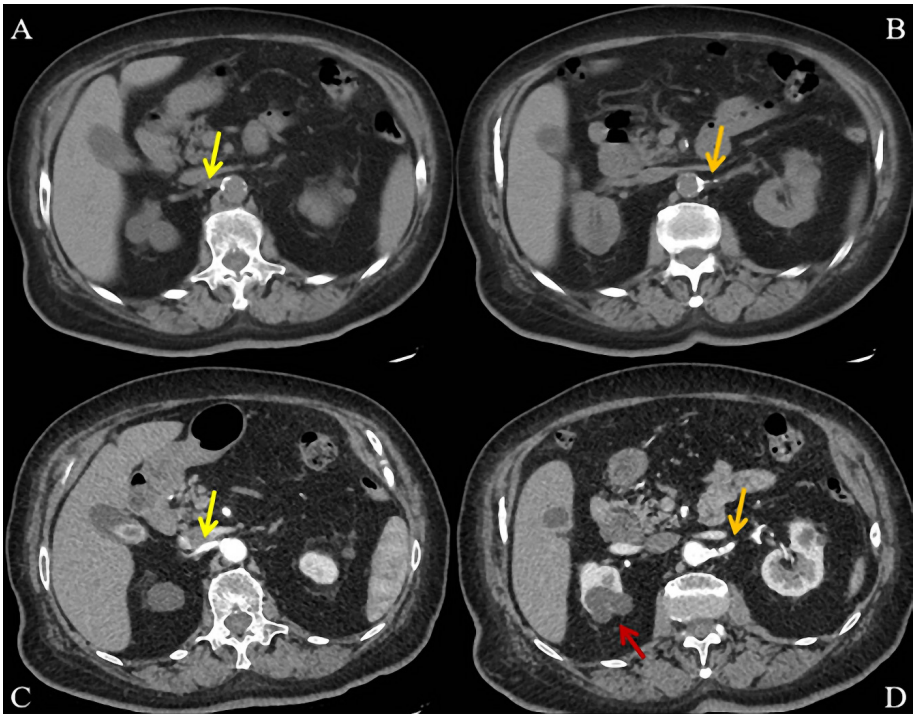

Figure 4 A-D. Abdomino-pelvic computed tomography. Calcifications of the abdominal aorta and of the right (A) and left (B) renal arteries at the origin on examination without i.v. contrast. Examination with i.v. contrast revealing ostial stenosis of the right (C) and left (D) renal arteries and a cortical renal cysts (D - red arrow).

that the cause of the inadequate BP control included a combination of suboptimal treatment selection and titration, along with persistent causes of hypertension such as atherosclerotic renovascular disease and sleep apnoea. We could not exclude primary hyperaldosteronism considering the small area of cortical hyperplasia in the left adrenal gland and mild hypokalaemia, as the hormonal dosage was not available.

The treatment approach combined reinforcement of lifestyle measures with antihypertensive drugs, which included a single-pill combination of an angiotensin receptor blocker - ARB (valsartan 160 mg b.i.d), a calcium channel blocker (CCB) (amlodipine 10 mg o.d.) and a thiazide diuretic (hydrochlorothiazide 25 mg o.d.), along with a low-dose antialdosterone diuretic (spironolactone 25 mg o.d.), beta-blocker (metoprolol succinate 50 mg o.d.) and central inhibitor of alpha-adrenergic receptors (methyldopa 250 mg t.i.d). Under this treatment regimen, optimal BP control was obtained at the one-month follow-up: the mean 24h

BP was 133/63 mmHg on ABPM. The treatment also included anticoagulant therapy (apixaban 5 mg b.i.d) for stroke prevention considering the high CHA2DS2-VASc score, with a value of 6, and the intermediate bleeding risk (HAS-BLED score with a value of 2). Statin therapy was associated (atorvastatin 20 mg o.d.) with an LDL-c target of <55 mg/dL.

Our patient associated symptomatic high-gradient severe aortic stenosis; therefore, she had a class I, level of evidence B indication for aortic valvular replacement. In view of a possible valvular intervention in a patient with multiple cardiovascular risk factors, coronary angiography was performed, showing an 80% stenosis of the mid-left anterior descendent (LAD) artery. Transcatheter aortic valve implantation (TAVI) and LAD stent placement were proposed, but the patient declined the intervention opting for conservative management.

Discussions

If we ought to choose a word to describe this case, it would be "severe", as we are facing an old patient with severe aortic stenosis and difficult-to-treat severe arterial HTN, which poses a lot of questions and difficulties regarding management.

We presented a patient with the implausible association between severe HTN and severe aortic stenosis, a patient with several possible causes of secondary HTN such as bilateral moderate renal arteries stenosis, chronic kidney disease (CKD), obstructive sleep apnoea (OSA), hyperplasia of an adrenal gland, and multiple comorbidities (previous ischemic strokes, paroxysmal atrial fibrillation and systemic atherosclerosis - carotid artery disease, renal arteries disease and coronary artery disease).

Currently, there are no dedicated guidelines on the management of arterial hypertension in valvular heart disease [5]. However, in 2020, the European Society of Cardiology published the first consensus document on the management of patients with combined arterial HTN and aortic valve stenosis, which reports experts' opinion due to lack of data from randomized trials [1].

In order to confirm and refine the diagnosis of arterial HTN in patients with aortic stenosis and optimize management, ABPM may be considered besides conventional office BP measurement. Initiating drug treatment for arterial HTN in patients over 80 years with aortic stenosis, such as our case, is recommended if BP is above 140/90 mmHg and the patient is symptomatic. If the patient is asymptomatic, the cut-off is 160/90 mmHg at this age [1]. It seems that the optimal therapeutic target is consistent with the general indications from the 2018 ESC/ESH Guidelines on HTN, with no age restriction. A systolic BP of 130-139 mmHg and a diastolic BP of 70-79 mmHg seem to be associated with the lowest rate of cardiovascular morbidity and all-cause mortality. However, their value must not fall under 120/70 mmHg [1, 5].

The co-existence of these diseases is associated with higher global LV pressure overload, more abnormal geometry and function of the LV, and more unsatisfactory cardiovascular outcome [1, 3, 6]. Thus, BP control is essential but difficult to obtain as the management of arterial HTN in aortic stenosis generated some concerns regarding the potential adverse consequences of drug-induced peripheral vasodilatation [1, 5, 6].

The prevalent hesitation in achieving target BP values in patients with aortic stenosis results from the now obsolete notion that obstruction at the valve level is the most important cause of increased LV load and that, facing this fixed afterload, cardiac output cannot be augmented. Given this flawed theory, the traditional teaching was that vasodilators are contraindicated in aortic stenosis because they lead to a decrease in systemic vascular resistance without a compensatory increase in cardiac output, thus precipitating hypotension [8].

Nevertheless, current evidence suggests that many patients, especially the elderly, remain uncontrolled with deleterious effects for the LV, whereas hypotension is rarely seen. Drugs blocking the renin-angiotensin-aldosterone system (RAAS) are first-line treatment, adding further drug classes when required. General guideline recommendations should be followed, but care should be taken to avoid hypotension in patients with severe and/or symptomatic aortic stenosis, known heart failure, or left ventricle systolic dysfunction [1].

Neuroendocrine activation is well demonstrated in aortic stenosis, RAAS being responsible for the development of LV hypertrophy and myocardial fibrosis. Arterial HTN is also associated with neuroendocrine activation, but the molecular mechanisms are incompletely studied when these two pathologies coexist. Nevertheless, antihypertensive drugs that block RAAS reduce LV hypertrophy and improve symptoms, functional capacity and survival, when given before or after surgery. Therefore, angiotensin-converting enzyme inhibitors (ACEI) such as enalapril, trandolapril, ramipril, or angiotensin II receptor blockers (ARBs) are first-line therapy, although randomized controlled studies are limited, and these data derive mainly from observational studies [1, 5, 6]. Contrary to expectations, a meta-analysis suggests that the benefit of RAAS inhibitors may be most substantial in those with critical or severe aortic stenosis with hemodynamic compromise [6].

Together with RAAS, the sympathetic nervous system is activated, increasing heart rate and BP and predisposing to myocardial ischemia. Adding β-blockers to therapy may be considered, especially in patients with compelling indications (coronary

artery disease, arrhythmias, left ventricular dysfunction) [1, 5, 6].

Diuretics should be carefully used in patients with concentric hypertrophy and small left ventricle cavity, although they may be beneficial on short-term for symptom relief [1, 5].

There are still, however, many controversies around vasodilator antihypertensive therapies. Small studies have demonstrated the efficacy and safety of sodium nitroprusside in the acute setting. Other drugs, such as intravenous dihydropyridines, are contraindicated by the American guidelines for hypertensive emergencies in patients with advanced aortic stenosis [9]. Insufficient data is available regarding the long-term use of vasodilators, such as calcium channel blockers (CCB) and nitrates. There is some data regarding the potential increase in mortality associated with CCB. The EXTAS (Exercise Testing in Aortic Stenosis) observational study found an increase in all-cause mortality in patients treated with CCB (34% in patients with CCB vs. 23% in patients without CCB, p=0.049) over a median follow-up of 25 months. Thus, these drugs should not be considered a first-line treatment in hypertensive patients with aortic stenosis [1, 5, 6].

The alpha-blockers are another controversial class, as they were the only ones associated with a higher risk of ischaemic cardiovascular events in some studies, and they should be avoided [1, 5].

Even though the association between HTN and aortic stenosis is accepted as a frequent entity in the latest years, we could not find any significant data on the association of difficult-to-treat or resistant hypertension and aortic stenosis. In our case, BP targets were achieved using six drugs, with one being a diuretic, a scenario considered improbable in the presence of severe aortic stenosis.

Resistant hypertension (R-HTN) is defined as the impossibility to achieve target BP (less than 140/90 mmHg) despite optimal doses (or best-tolerated doses) of an appropriate therapeutic strategy, which should include a diuretic (typically an ACEI or an ARB with a CCB and a thiazide/thiazide-type diuretic). R-HTN is defined only after the inadequate control of BP has been confirmed by ABPM or home BP measurement (HBPM) and after the exclusion of various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension. The term "controlled R-HTN" is used when BP targets are achieved using three or more drugs, with one being a diuretic [3, 10]. However, in our case, several potential causes for secondary hypertension were found – bilateral renal artery stenosis, CKD, mild OSA, and hyperplasia of one of the adrenal glands with possible hyperaldosteronism. Indeed, the prevalence of primary hyperaldosteronism in the population of R-HNT is found to be as high as 20% but frequently remains undiagnosed or incorrectly confirmed, as in our case [11]. Nonetheless, spironolactone has been proven efficient in both R-HTN and primary hyperaldosteronism in controlling BP values and is the mainstay therapy in such cases. Indeed, HTN guidelines are currently recommending spironolactone as the fourth drug (after ACEI or ARB, CCB, and thiazide or thiazide-like diuretics) for the treatment of R-HTN and was added to our patient's therapeutic plan with good results [3].

Considering the symptomatic high-gradient severe aortic stenosis, the patient we presented had an indication for prompt referral to a clinic for aortic valve replacement. Pre-operative management of hypertension in these patients is essential regarding mortality risk, irrespective of the chosen procedure. Following aortic valve intervention, especially after TAVI, a rise in systolic BP can occur, which may be enhanced by stiff large arteries, requiring short-term and, sometimes, long-term treatment. A meta-analysis found a statistically significant reduction in mortality when antihypertensive treatment was used post-aortic valve replacement [1, 5, 6].

Our patient declined any interventional treatment, and we proceeded with conservative treatment, which led to symptom improvement.

Indeed, symptoms of aortic stenosis develop with a larger aortic valve area (AVA) in patients with uncontrolled hypertension. As a consequence, in patients with coexisting hypertension and aortic stenosis, hypertension should be treated more aggressively to delay the occurrence of symptoms, and these patients should be followed up more closely. Moreover, as hypertension has been associated with a faster progression of aortic stenosis severity, in the earlier stages of aortic stenosis, better BP control becomes mandatory [12].

Conclusion

We presented a case that defies the misconception that severe aortic stenosis and severe hypertension cannot coexist. Aortic stenosis and hypertension occur commonly as a duo, and optimal BP control is mandatory in order to reduce cardiovascular morbidity and mortality in aortic stenosis patients. Appropriate selection of BP-lowering drugs, adjustment of BP targets to the patient's risk profile, and close follow-up remain the cornerstones of hypertension treatment in aortic stenosis patients.

Conflict of Interest

The author confirms that there are no conflicts of interest.

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