Caught between a rock and a hard place: a patient with aortic valve stenosis and phaeochromocytoma

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An 81-year-old man was admitted to the intensive care unit for preoperative medical treatment aimed at controlling hypertension and tachycardia. A year earlier, he had been referred to a cardiologist regarding a heart murmur. He was diagnosed with severe aortic valve stenosis, with an aortic valvular area of 1.1 cm² and a mean gradient of 57 mmHg. During the workup a CT scan revealed a mass in the left adrenal gland with a diameter of 4.5 cm, suggestive of a phaeochromocytoma. Excessive production of noradrenaline and dopamine was demonstrated as the blood analysis showed high levels of normetanephrines (4.72 nmol/l, normal range 0.23-1.07 nmol/l) and 3-methoxytyramine (0.10 nmol/l, normal range 0.00-0.04 nmol/l), respectively. Both MIBG and FDG-PET scans were compatible with phaeochromocytoma without metastatic disease.

This elderly man seems to have both aortic valve stenosis and phaeochromocytoma. The aortic valvular area of 1.1 cm² in itself does not classify as severe aortic stenosis, but as the mean transaortic pressure gradient is far above 40 mmHg, this stenosis should be qualified as severe.[1] The prevalence of aortic stenosis is high (9.8%) in adults older than 80 years of age.[1] On the other hand, phaeochromocytoma is a rare tumour that is usually diagnosed in individuals aged 40-50 years.[2] The remarkable combination of aortic valve stenosis and phaeochromocytoma could result in opposing effects on the circulation, and produce overlapping symptoms. Typically, patients with phaeochromocytoma present with episodes of headaches, sweating, palpitations, and hypertension. However, the clinical presentation of phaeochromocytoma can vary greatly, with signs and symptoms also produced by many other clinical conditions, including heart failure and ischaemic heart disease.[1] In addition, some patients are asymptomatic and over the years; the number of asymptomatic patients has risen steadily due to the increased incidence of adrenal incidentalomas that are discovered during imaging studies for unrelated disorders.[1] Both aortic valve stenosis and phaeochromocytoma are associated with palpitations, chest pain, dyspnoea, dizziness, weakness and fatigue. It is important to review the complaints and vital signs of the patient in order to clarify whether both conditions are symptomatic or not.

The patient expressed complaints of severe dyspnoea on exertion and fatigue with a progressive limitation of exercise tolerance. He did not experience episodic symptoms such as headache, sweating, or tachycardia. His medical history included long-standing (primary) hypertension, diabetes mellitus type 2, stroke and prostate cancer.

These symptoms could very well originate from severe aortic stenosis.[1] Despite the demonstrated high catecholamine production, the phaeochromocytoma clinically appears to be an asymptomatic incidentaloma of the adrenal gland. Severe, high-gradient aortic stenosis is associated with high mortality (70-80% at two years) and aortic valve replacement (AVR) is the only effective therapy.[1] Aortic valve stenosis is not associated with phaeochromocytoma. However, some fatal complications during aortic valve surgery have been related to unsuspected phaeochromocytoma with symptoms masked by cardiac disease.[4] Morbidity and mortality associated with aortic valve replacement in high-risk patients are high. In a recent trial, 3-year all-cause mortality or stroke in patients who had undergone open surgical valve replacement was 47%.[5] This prospective study demonstrated a more favourable outcome in high-risk patients after transcatheter aortic valve implantation (TAVI) with a 10% lower 3-year all-cause mortality or stroke risk.[5] Thus, in this elderly patient with severe comorbidity, TAVI is to be preferred over valve replacement by open heart surgery. Balloon dilatation of the aortic valve is not a definitive therapy as it provides only temporary and limited haemodynamic benefit, which is offset by the substantial risk of procedural complications.[1] However, this procedure can be an acceptable...
A patient with aortic valve stenosis and pheochromocytoma

While surgical treatment of the symptomatic aortic valve stenosis is inevitable, the urgency of resection of the adrenal mass is much less clear for this elderly patient. Generally, resection of pheochromocytomas is recommended for several reasons. High cardiovascular morbidity and mortality associated with hypersecretion of catecholamines is an important argument for resection. Also, these tumours grow over time and may cause mass-effect symptoms. Another reason for surgery is that 10 to 17% of pheochromocytomas are malignant or show a tendency to become malignant.

In this patient no evidence of metastatic disease was detected, but as a result of the demonstrated excessive catecholamine release, surgical removal of the adrenal mass was considered strongly indicated. Several strategies should be considered: 1) adrenalectomy followed by TAVI in two separate sessions; 2) TAVI followed by adrenalectomy in two separate sessions; 3) both procedures during one session; or 4) balloon dilatation followed by adrenalectomy and then followed by TAVI. If adrenalectomy is attempted as primary treatment, haemodynamic instability due to tumour manipulation, with release of catecholamine, would be of great concern. Tachycardia would probably be poorly tolerated due to diastolic dysfunction in the setting of left ventricular hypertrophy and severe aortic stenosis.

This could result in a decrease in general organ perfusion, most notably detrimental for cerebral perfusion. Due to an increase in coronary oxygen consumption, the risk for cardiac ischaemia would be of great concern as well. On the other hand, conducting a TAVI procedure before abdominal surgery could trigger an adrenergic crisis, possibly leading to heart failure and multi-organ failure.

After careful consideration, the decision was made to first attempt a TAVI procedure and to plan a subsequent adrenalectomy. The patient was admitted to the ICU for treatment preceding the TAVI. On physical examination at admission his blood pressure was 169/62 mmHg (in sitting position) and he had a regular pulse of 80/minute. Hypertension treatment, as prescribed by his primary care physician, consisted of amlodipine, irbesartan and furosemide. Doxazosin was initiated three weeks previously at a dosage of 8 mg per day.

The current guideline for perioperative management of phaeochromocytoma recommends preoperative blockade with an alpha-adrenergic receptor blocker, such as doxazosin.

The aim of treatment should be to achieve maximum alpha blockade, without resulting in overt orthostatic hypotension and subsequent risk of hypoperfusion. Blood pressure reduction is considered adequate if the patient is free of symptoms with a blood pressure of less than 130/80 mmHg and a heart rate of 60-70 beats per minute in a seated position and a systolic blood pressure of more than 90 mmHg and a heart rate of 70-80 beats per minute in standing position. Normally, we would have stopped the furosemide and other antihypertensive drugs in order to be able to increase the dose of doxazosin. However, considering the patient’s severe aortic stenosis, in which an adequate preload and an elevated afterload are desirable, treatment according to this protocol could lead to cardiac ischaemia and hypoperfusion of several organs. Therefore, additional treatment with metyrosine was proposed in order to further stabilise the blood pressure and decrease the necessary dosage of doxazosin. Metyrosine is a tyrosine hydroxylase inhibitor that directly reduces catecholamine biosynthesis and may be used in combination with α-adrenergic receptor blockers for a short period before surgery to further stabilise blood pressure to reduce blood loss and volume depletion during surgery.

Treatment with metyrosine was commenced, doxazosin was continued and irbesartan, amlodipine and furosemide were discontinued. On day 3 after initiation of metyrosine the patient’s blood pressure dropped to 104/33 mmHg in a supine position. Shortly after the introduction of metyrosine the patient developed delirium. He also experienced extreme drowsiness. Furthermore, acute kidney injury developed.

Somnolence and delirium can be attributed to the use of metyrosine. Several central nervous system effects have been observed, in some patients even at low dosages of metyrosine. Somnolence is the most frequent side effect of metyrosine; even at low doses some degree of sedation or feeling of fatigue may occur. Bizarre dreams, visual hallucinations, anxiety and psychosis are associated with higher doses. In this case delirium could also be attributable to cerebral hypoperfusion; however, the time-relationship suggests a putative effect of metyrosine. Although no extreme drop in blood pressure occurred, the patient developed a decline in renal function. Apparently renal perfusion has been insufficient for some period of time as renal and post-renal causes were unlikely to play a role.

Eight days after ICU admission, a transfemoral aortic valve replacement was performed. During the procedure, the blood pressure varied with a systolic between 100-180 mmHg and a diastolic of 20-40 mmHg necessitating vasopressor treatment with norepinephrine and phenylephrine. No further complications occurred during the procedure. A day after the procedure the patient was discharged from the ICU to the general ward in a fairly good condition. His blood pressure continued to be somewhat elevated and the delirium persisted. Treatment with metyrosine was discontinued and the dose of doxazosin was augmented. Furthermore diuretic therapy was re-introduced to correct fluid retention. After a full recovery of his delirium the patient was discharged. One
month later he was seen at the outpatient clinic. His condition had improved considerably and he was still free of episodic symptoms which could be related to pheochromocytoma. For that reason he currently refrains from surgical removal of the adrenal tumour.

**Commentary**

Pheochromocytoma is a rare condition, especially in the elderly. Unrecognised pheochromocytoma is associated with a high risk of major complications for patients who undergo anaesthesia, which is a well-known trigger for a catecholaminergic crisis. This results in severe hypertension, cardiac arrhythmias, pulmonary oedema, cardiac ischaemia and cardiovascular collapse occurring after induction of anaesthesia or at any time during the procedure. In this case the adrenal tumour was discovered incidentally during the TAVI workup that includes CT angiography to assess suitability for a percutaneous transfemoral TAVI approach. However, finding the optimal treatment for a patient with both pheochromocytoma and severe aortic valve stenosis is difficult. Preoperative treatment strategies are challenging due to the different end goals in both entities. Alpha blockade is the treatment of choice for pheochromocytoma, reducing the risk of an adrenergic crisis. In aortic stenosis, however, there is a relatively fixed afterload - meaning cardiac output does not increase with reduction of afterload. Therefore, all afterload-reducing agents (angiotensin-converting enzyme inhibitors, calcium channel blockers, beta blockers and alpha blockers) can lead to a decrease in coronary blood flow increasing the risk of cardiac ischaemia.

Multidisciplinary effort of different medical specialties such as cardiologists, endocrinologists, cardiothoracic surgeons and intensivists is paramount. Different treatment modalities should be extensively considered. In this specific case the patient was treated with metyrosine to decrease the side effects of alpha blockade, specifically tachycardia but also afterload reduction, which could be detrimental with aortic valve stenosis. Administration of metyrosine, a tyrosine hydroxylase inhibitor, reduces catecholamine biosynthesis by 35-80%, and can be used in the preoperative treatment of pheochromocytoma. Treatment with beta blockers, mainstay in the treatment of aortic valve stenosis as rate control for arrhythmias, such as atrial fibrillation, was not warranted in this patient as it might result in unopposed alpha-mediated vasoconstriction. Preoperative pharmacological treatment resulted in symptoms of decreased systemic blood pressure, such as a decrease in urinary output with a concomitant increase in creatinine values. It has been shown that adrenal surgery for elderly patients can be performed with acceptable morbidity and mortality. However, no data are available concerning conservative management of (asymptomatic) pheochromocytoma in the elderly. Thus, whether an operation in this patient category is better than long-term medical treatment with alpha blockers is not at all clear. Likewise, the patient’s decision in this case not to proceed with surgical removal of the tumour may be wise.

In summary, treatment of a patient with pheochromocytoma and severe aortic stenosis requires intensive haemodynamic monitoring and tapered treatment during the pre-procedural course to minimise complications. A personalised approach to the elderly patient is crucial.

**Disclosures**

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**References**