Pulmonary hypertension: a contraindication to the use of β-adrenoceptor blocking agents

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ABSTRACT
Supraventricular tachycardia (SVT) is a rare but important complication of pulmonary arterial hypertension. β-Adrenoceptor blocking agents are commonly used to treat SVT, but they are potentially dangerous in the context of pulmonary arterial hypertension. Their negative inotropic and chronotropic effects are poorly tolerated in this condition, where cardiac reserve is compromised by a reduced and fixed stroke volume, and their administration can result in significant cardiorespiratory compromise. This is not a new discovery, but it is nonetheless poorly recognised in day-to-day clinical practice.

CASE HISTORY
The patient presented with portopulmonary hypertension secondary to alcoholic liver disease diagnosed 2 years previously by echocardiography and cardiac catheterisation (mean pulmonary artery pressure 40 mm Hg, pulmonary capillary wedge pressure 6 mm Hg, pulmonary vascular resistance 11.3 WU, cardiac index 1.9 l/min/m²). She had a background of alcohol excess and liver cirrhosis for which she had undergone a transjugular intrahepatic portosystemic shunt procedure 15 years earlier. No further factors were identified that could have contributed to the pulmonary hypertension and her only other medical history of note was a recent pulmonary embolism, treated with 3 months of warfarin, and episodic supraventricular tachycardia (SVT).

She had been discharged from the Scottish Pulmonary Vascular Unit (SPVU) 1 week previously following a review admission. Her clinical condition had remained relatively stable since her diagnosis but she had dyspnoea and a decision was made to add sildenafil. She was taking sildenafil 50 mg three times daily and bosentan 62.5 mg twice daily, a reduced dose due to the introduction of sildenafil.

Within 48 h of discharge from the SPVU she developed symptoms of increasing dyspnoea, vomiting, periorbital and upper limb swelling, left-sided chest pain and abdominal distension. Four days later she presented to a district general hospital emergency department with saturations of 92% on 10 l oxygen, heart rate 94 beats/min and blood pressure 147/92 mm Hg. She was dyspnoeic with clear lungs, cool peripheries, oedema and a raised jugular venous pressure. Arterial blood gas analysis on 10 l oxygen showed H+ 42 nmol/l, PO2 92% on 10 l oxygen, heart rate 94 beats/min and blood pressure 147/92 mm Hg. She was dyspnoeic with clear lungs, cool peripheries, oedema and a raised jugular venous pressure. Arterial blood gas analysis on 10 l oxygen showed H+ 42 nmol/l, PO2 92% on 10 l oxygen, heart rate 94 beats/min and blood pressure 147/92 mm Hg. She was dyspnoeic with clear lungs, cool peripheries, oedema and a raised jugular venous pressure. Arterial blood gas analysis on 10 l oxygen showed H+ 42 nmol/l, PO2 92% on 10 l oxygen, heart rate 94 beats/min and blood pressure 147/92 mm Hg.
DISCUSSION
Pulmonary arterial hypertension (PAH) is a recognised complication of portal hypertension secondary to cirrhosis. Although rare, it is a cause of significant morbidity and mortality. Patients exhibit extensive pulmonary vascular remodelling, increased pulmonary vascular resistance and right heart failure. It is diagnosed against a background of cirrhosis with elevated right ventricular pressures on echocardiography, and confirmed by right heart catheterisation which demonstrates mean pulmonary artery pressure $>$25 mm Hg.

The potential detrimental effects of beta-blocker blockers in PAH are poorly recognised in day-to-day clinical practice. Indeed, our review of the literature yielded just one directly relevant paper. This study observed the effect of beta-blocker withdrawal at 2 months in patients with PAH receiving beta-blockers for prophylaxis of variceal bleeding. It reported improvements in pulmonary haemodynamics, exercise capacity, 6-min walking distance and cardiac output, with decreased pulmonary vascular resistance.

Beta-blockers are competitive antagonists of the effect of catecholamines at beta-adrenoceptor sites with resultant negative inotropic and chronotropic effects. They are generally well tolerated and adverse effects are transient but, in sensitive patients or following larger doses, severe cardiovascular depression has been reported. Adverse effects include deterioration in right ventricular function, severe hypotension, bradycardia, increased ventilation-perfusion mismatch and hypoxaemia. In PAH, where cardiac reserve is already compromised by a reduced xed stroke volume, the additional chronotropic depression imposed by beta-blockers can result in significant or, indeed, fatal cardiovascular compromise.

When beta-blockers are used in combination with other antiarrhythmic agents or drugs affecting cardiac conduction, the potential for precipitating bradycardia and heart block is increased. Bradycardia, cardiac arrest and ventricular fibrillation have all been reported on starting beta-blockers in patients receiving amiodarone. Of note, amiodarone has been shown to increase plasma concentrations of metoprolol.

SVT is an important but rare complication of PAH secondary to right-sided atrial and ventricular enlargement as a result of chronic pressure overload. A single-centre study by Tongers et al found it to have a cumulative incidence of 11.7% and an annual risk of 2.8% per patient. Its onset is generally associated with right ventricular failure and results in marked clinical deterioration. The final clinical outcome varies with different types of SVT. Atrial flutter and atrioventricular nodal re-entry tachycardia are more likely to be restored to sinus rhythm with appropriate therapeutic intervention, whereas atrial fibrillation, if sustained, has a high associated mortality.

Treatment options for SVT in this context are interventional or medical. Interventional approaches include overdrive pacing, radiofrequency ablation and electrical cardioversion. Although effective, these require adequate specialised equipment, staffing and training, and are not generally an option at 03:00 in a district general hospital. Medical options include adenosine, amiodarone, the calcium channel antagonist verapamil, digoxin and beta-adrenoceptor blockers. Each has its drawbacks. While adenosine and verapamil are commonly used to treat SVT in the emergency department, the former is associated with a significant incidence of unpleasant side effects and the latter can result in hypotension. Digoxin has a narrow therapeutic index and amiodarone is associated with a host of adverse effects, notably interstitial lung disease and significant liver injury, especially after prolonged usage.

As acknowledged by Tongers et al, there is a lack of evidence to fully understand the incidence, consequences and optimal treatment options for SVTs in PAH.

In conclusion, in an attempt to control SVT, a rare but important complication of PAH, our patient was given a small dose of a short-acting beta-adrenoceptor blocking agent, the effects of which may have been potentiated by the simultaneous administration of amiodarone. The cardiovascular depression provoked was not tolerated by a heart impaired by portopulmonary hypertension. In the setting of a fixed reduced stroke volume, suppression of the chronotropic response resulted in insufficient cardiac output to maintain clinical stability.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES