Transient platypnea-orthodeoxia-like syndrome induced by propafenone overdose in a young woman with Ebstein's anomaly

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In this report we describe the case of a 37-year-old white woman with Ebstein's anomaly, who developed a rare syndrome called platypnea-orthodeoxia, characterized by massive right-to-left interatrial shunting with transient profound hypoxia and cyanosis. This shunt of blood via a patent foramen ovale occurred in the presence of a normal pulmonary artery pressure, and was probably precipitated by a propafenone overdose. This drug caused biventricular dysfunction, due to its negative inotropic effect, and hypotension, due to its peripheral vasodilatory effect. These effects gave rise to an increase in the right atrial pressure and a decrease in the left one with a consequent stretching of the foramen ovale and the creation of massive right-to-left shunting. In our case this interatrial shunt was very accurately detected at bubble contrast echocardiography.

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Introduction

Ebstein's anomaly is a well-known abnormality of the tricuspid valve, which is displaced downwards into the right ventricle. Thus, the inflow tract of the right ventricle is "atrialized" and the remaining functional portion is small[1]. In approximately 80% of these patients an interatrial communication, a patent foramen ovale (PFO) or an atrial septal defect, is present[1]. Under normal conditions this communication allows blood to shunt from left to right due to a higher pressure in the left atrium than the right atrium and a greater compliance of the right ventricle as compared to the left ventricle. If pulmonary hypertension is concomitant with cardiac or pulmonary disease, an acute or chronic right-to-left interatrial shunt may develop. When transient massive right-to-left interatrial shunting occurs in the presence of a normal pulmonary artery pressure, a rare syndrome, called platypnea-orthodeoxia, ensues[2]. This is characterized by dyspnea and deoxygenation, induced by the upright posture and relieved by recumbency. Since Burchell et al. described this rare syndrome over half a century ago, no more than 50 cases have been reported in the literature and none in patients with Ebstein's anomaly[2].

In this report we describe a patient with Ebstein's anomaly, who developed transient profound hypoxia, cyanosis and right-to-left shunting at the atrial level, probably due to a propafenone overdose.

Case report

A 37-year-old white woman (weight 39 kg, height 157 cm, body mass index 16 kg/m^2) affected by Ebstein's anomaly presented with a 21-year history of paroxysmal supraventricular tachycardia. The arrhythmia was initially treated with amiodarone (200 mg daily) and then, due to the development of mild hypothyroidism, with propafenone (450 mg daily). The day of admission she began to complain of tachyarrhythmic palpitations and for this reason she took 300 mg of propafenone. A few hours later, owing to the persistence of symptoms, she assumed a further 600 mg of propafenone (a total dose of 900 mg within 11 hours). She then presented with incapacitating fatigue, nausea, abdominal pain and pre-syncope associated with vomiting. Physical examination at the time of the patient's arrival to the emergency room revealed severe dyspnea, cold sweating, cyanosis and paleness. The pulse rate was approximately 80 b/min and her blood

pressure was 70/40 mmHg. Cardiac examination revealed splitting of both heart sounds and a 3/6 systolic murmur on the left lower sternal border. The jugular venous pressure was evidently increased. Thoracic examination was unremarkable. The electrocardiogram (ECG) (Fig. 1) showed sinus rhythm at a rate of 85 b/min with first degree atrioventricular block (PQ 240 ms), signs of right atrial enlargement, complete right bundle branch block with a wide QRS (150 ms) and non-specific alterations of repolarization. An arterial blood gas determination on room air showed a pH 7.39, a PO_2 of 32.5 mmHg, a PCO_2 of 23 mmHg, an HCO_3^- concentration of 13.7 mmol/l, a base excess of -9 mmol/l and an oxygen saturation of 64%. At chest X-ray the lungs appeared clear and the heart enlarged. Transthoracic echocardiography showed that the left heart chambers and the aortic valve were normal. There was a mild mitral valve prolapse with trivial mitral regurgitation. An anatomical downward displacement and distortion of the tricuspid valve leaflets (septal and posterior) was evident. The anterior leaflet was excessively large and prolapsed into the atrium, with severe tricuspid regurgitation at a velocity of 1.8 m/s (suggesting a normal pulmonary artery pressure). There was an atrialized portion of the right ventricle which was dilated and characterized by a paradoxical septal movement, and a mild right atrial enlargement. Color Doppler imaging showed significant right-to-left interatrial shunting. This shunt was confirmed at echocontrast with repeated peripheral injections of 5% dextrose through an antecubital vein, which demonstrated a massive passage of microbubbles from the right to the left atrium through a wide PFO (Fig. 2). This shunt simulated the modalities of shunting of the fetal circulation.

Because of systemic hypotension, probably related to the propafenone overdose, the patient was treated with plasma expanders, dopamine (8 γ/kg/min) and dobutamine (3.3 γ/kg/min). Her blood pressure rose to 103/74 mmHg. About 1 hour later the patient developed convulsions associated with sinus tachycardia at 110 b/min and hypotension (70/40 mmHg). The ECG (Fig. 3) had deteriorated and showed sinus rhythm at a rate of 90 b/min with first degree atrioventricular block (PQ 280 ms), a long QT (rate-corrected QT interval 487 ms), and complete right bundle branch block with further widening of the QRS (180 ms). The patient required tracheal intubation and assisted ventilation. Within a few hours the situation stabilized and spontaneous ventilation started anew. The pulse rate was 85 b/min and her blood pressure was 100/60 mmHg. On 100% oxygen, the pH was 7.3, the PO_2 was 87 mmHg, the PCO_2 was 35.3 mmHg, the HCO_3^- concentration was 17.8 mmol/l, the base excess was -7.1 mmol/l, and the oxygen saturation was 95.7%. During the following hours the patient was extubated, inotropic drugs were first reduced and then discontinued (the blood pressure was 110/70 mmHg) and plasma expanders were continued to increase the circulating volume.

The day after the patient had no signs of heart failure and an unchanged cardiac evaluation. No arrhythmias were documented. The ECG (Fig. 4) revealed sinus rhythm at a rate of 80 b/min and right bundle branch block with a shortened QRS (120 ms). The first degree atrioventricular block had regressed (PQ 210 ms) but

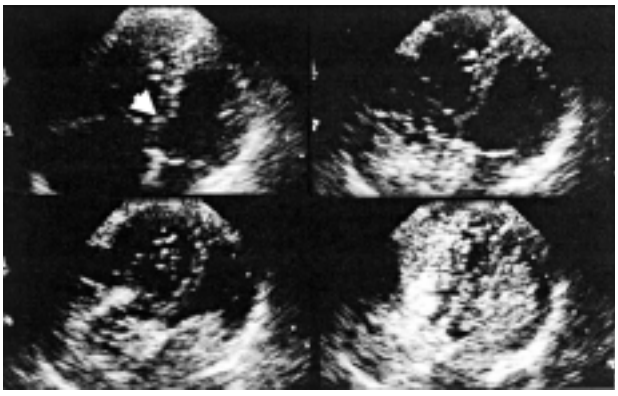

Figure 2. *Echocontrast demonstrated the massive passage of microbubbles from the right to the left atrium through the patent foramen ovale.*

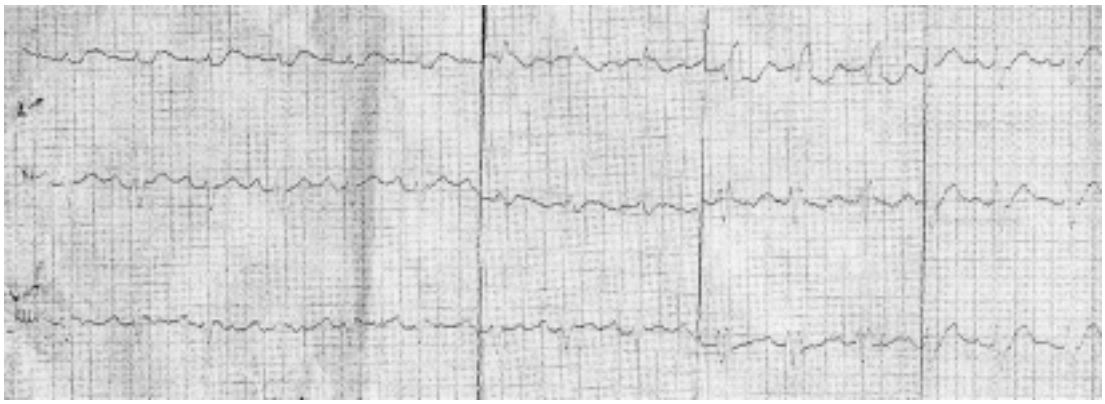

Figure 1. *Electrocardiogram at admission.*

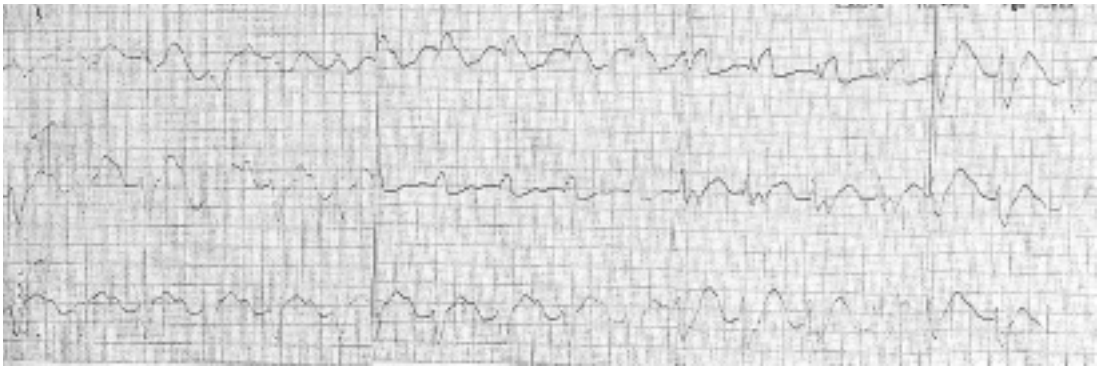

Figure 3. *Electrocardiogram with signs of propafenone intoxication.*

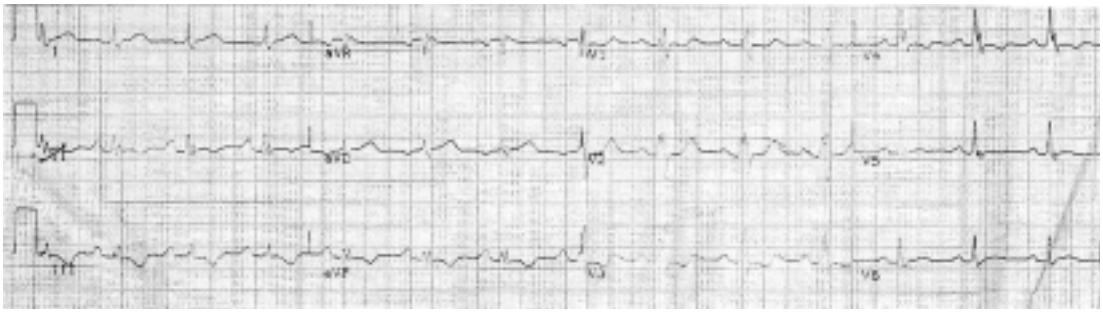

Figure 4. *Electrocardiogram at discharge.*

the long QT persisted, even though the QT interval was shorter (rate-corrected QT interval 410 ms). On 100% oxygen, the pH was 7.34, the PO_2 290 mmHg, the PCO_2 33.6 mmHg, the HCO_3^- concentration 23.2 mmol/l, the base excess -0.4 mmol/l, and the oxygen saturation 100%. Transthoracic echocardiography and color Doppler confirmed the presence of a wide PFO and the persistence of severe tricuspid regurgitation at a velocity of 2.6 m/s. Contrast echocardiography performed during coughing and the Valsalva maneuver confirmed the absence of any right-to-left shunt of microbubbles. Thereafter the patient's recovery was uneventful. The patient was discharged without symptoms and on a therapeutic regimen of amiodarone (200 mg daily), in spite of her history of mild hypothyroidism. At 6 months of follow-up the patient was asymptomatic, and no arrhythmia was documented at Holter analysis.

Discussion

Under normal conditions an interatrial communication allows blood to shunt from the left to the right due to a higher pressure in the left atrium than the right atrium and a greater compliance of the right ventricle than the left. An acute right-to-left interatrial shunt is usually associated with spontaneous or induced pulmonary hypertension consequent to a cardiac or pulmonary insult[3]. A PFO, which occurs in approximately 30% of the adult population, is present in the majority of reported cases of an acute right-to-left interatrial shunt[1].

In our case the patient was affected by Ebstein's anomaly, which is an abnormality of the tricuspid valve in which the septal leaflet and often the posterior leaflet are displaced downwards into the right ventricle. Thus, a portion of the right ventricle is "atrialized" and the remaining functional portion is small[1]. Eighty percent of patients with Ebstein's anomaly have an interatrial communication (atrial septal defect or PFO) through which right-to-left shunting may occur[4]. Transient massive right-to-left shunting of blood via an interatrial communication in the presence of a normal pulmonary artery pressure occurs in a rare syndrome which is characterized by flat breathing and arterial oxygen desaturation, worsened by the upright posture and relieved by recumbency[3,5]. This syndrome, which is called platypnea-orthodeoxia, is due to the coexistence of two conditions: an anatomical component in the form of an interatrial communication and a functional component that produces a deformity of the atrial septum resulting in a redirection of flow with the assumption of the upright posture[2]. Standing upright could stretch the interatrial communication, PFO or atrial septal defect, thus allowing more streaming of venous blood from the inferior vena cava through the defect, regardless of the presence of a persistent Eustachian valve. It has been found that 20% of normal persons have a valve-compe-

tent foramen ovale. This is usually physiologically insignificant because the higher left atrial pressure maintains the valvular foramen ovale closed. However, with an enlarged right atrium the foramen ovale may be stretched enough to form a PFO. As a consequence the "ventricularized" right atrial pressure due to tricuspid insufficiency may cause right-to-left shunting. Furthermore, the limbus of the foramen ovale lies at the mouth of the inferior vena cava, allowing a direct passage of venous blood into the left atrium. This simulates the shunting in the fetal circulation[6].

The definitive diagnosis of platypnea-orthodeoxia syndrome is established by the demonstration of an orthostatic intracardiac shunt at Doppler echocardiography, and particularly at echocontrast. In fact, bubble contrast echocardiography is the most sensitive non-invasive technique for the detection of a right-to-left interatrial shunt. This test is positive if the passage of microbubbles to the left atrium is documented within two to three cycles of their initial appearance in the right atrium. This passage can be exacerbated when the intrathoracic pressure is increased during coughing or the Valsalva maneuver[1,2,4].

In our case report, the transient massive right-to-left shunting was due to biventricular dysfunction and to the severe tricuspid insufficiency associated with relative peripheral hypotension, which increases the right atrial pressure over the left atrial pressure, and to the enlarged right atrium, which stretches the foramen ovale leading to a wide PFO. Our case, similarly to that reported by Zerio et al.[7], suggests that in case of an acute elevation of the right heart pressure, a functionally closed PFO may eventually open providing a substrate for right-to-left shunting. Following the resolution of the relative peripheral hypotension and the decrease in the right heart pressure, a significant decrease in shunting through the PFO may occur, as demonstrated by the absence of any passage of microbubbles during contrast echocardiography performed the day after. In our case, the situation was precipitated by the propafenone overdose, that was probably responsible for the depressed right and left ventricular function due to both its negative inotropic effect and to the slowing down of the intraventricular conduction (appearance of right bundle branch block) as well as to its vasodilating properties causing hypotension[8]. These adverse effects depend on two mechanisms: the dose-dependent kinetics and the hepatic metabolism which transforms propafenone into its metabolite (5-hydroxypropafenone). The former is responsible for the disproportionate increase in plasma levels and for the peak in concentration following the overdose[8]. The latter explains why subjects with a deficiency of the microsomal enzyme P4502D6 (7% of the population), known as the poor-metabolizer phenotype, metabolize propafenone to its metabolite only to a very limited extent, with the result that their plasma propafenone levels are much higher and their plasma 5-hydroxypropafenone levels much lower than those of the remaining 93% of the population (who have the extensive metabolizer phenotype)[9].

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