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A sudden right-to-left shunt: the importance of evaluating patent foramen ovale during exercise

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Abstract

A 55-year-old male affected by heart failure with reduced ejection fraction and a history of a transient cerebrovascular accident was accepted to the Cardiology Department for worsening dyspnea. A cardiopulmonary exercise test was performed after therapy optimization to further evaluate exercise intolerance. A rapid increase in the minute ventilation/carbon dioxide production ratio, end-tidal oxygen pressure, and respiratory exchange ratio, with a concomitant decrease in end-tidal carbon dioxide pressure and oxygen saturation, were observed during the test. These findings indicate exercise-induced pulmonary hypertension leading to a right-to-left shunt. Subsequent echocardiography with a bubble test unveiled the presence of an unknown patent foramen ovale. It is, therefore, necessary to exclude a right-to-left shunt by cardiopulmonary exercise testing, particularly in patients predisposed to develop pulmonary hypertension during exercise. Indeed, this eventuality might potentially provoke severe cardiovascular embolisms. However, the patent foramen ovale closure in patients with heart failure with reduced ejection fraction is still debated because of its potential hemodynamic worsening.

Case Report

A 55-year-old male affected by heart failure (HF) with reduced ejection fraction (HFrEF) and a history of cardiovascular accident (CVA) was accepted to the Cardiology Department for worsening dyspnea during the last few months. He previously underwent implantation of a biventricular implantable cardioverter defibrillator (ICD) in primary prevention. Medical history included healthy coronary vessels at invasive coronary angiography. The patient was referred to our center to evaluate the dyspnea components and establish an etiology for the novel onset of left ventricular dysfunction. He underwent a coronary angiogram and right heart catheterization that showed no coronary artery disease and the presence of mild pulmonary hypertension (PH) at rest (mPAP 22 mmHg, pulmonary resistance 1,35 WU) with normal cardiac output (CO 7,40 l/min; cardiac index 3,47 (l*min*m^2). The Qp/Qs ratio was =1, indicating the absence of a shunt at rest. The transthoracic echocardiogram (TTE) showed a dilated left ventricle and global hypokinesia (LVEF of 35%). The ICD control demonstrated some episodes of ventricular tachycardia interrupted with anti-tachycardia pacing followed by 3 subsequent inappropriate shocks of atrial tachycardia. The medical therapy was further optimized during the stay, according to the latest European Society of Cardiology guidelines [1], including treatment with

angiotensin receptor-neprilysin inhibitor and sodium-glucose cotransporter 2-inhibitor. Before discharge, cardiopulmonary exercise testing (CPET) was performed to further assess the dyspnea and the cause of exercise limitation.

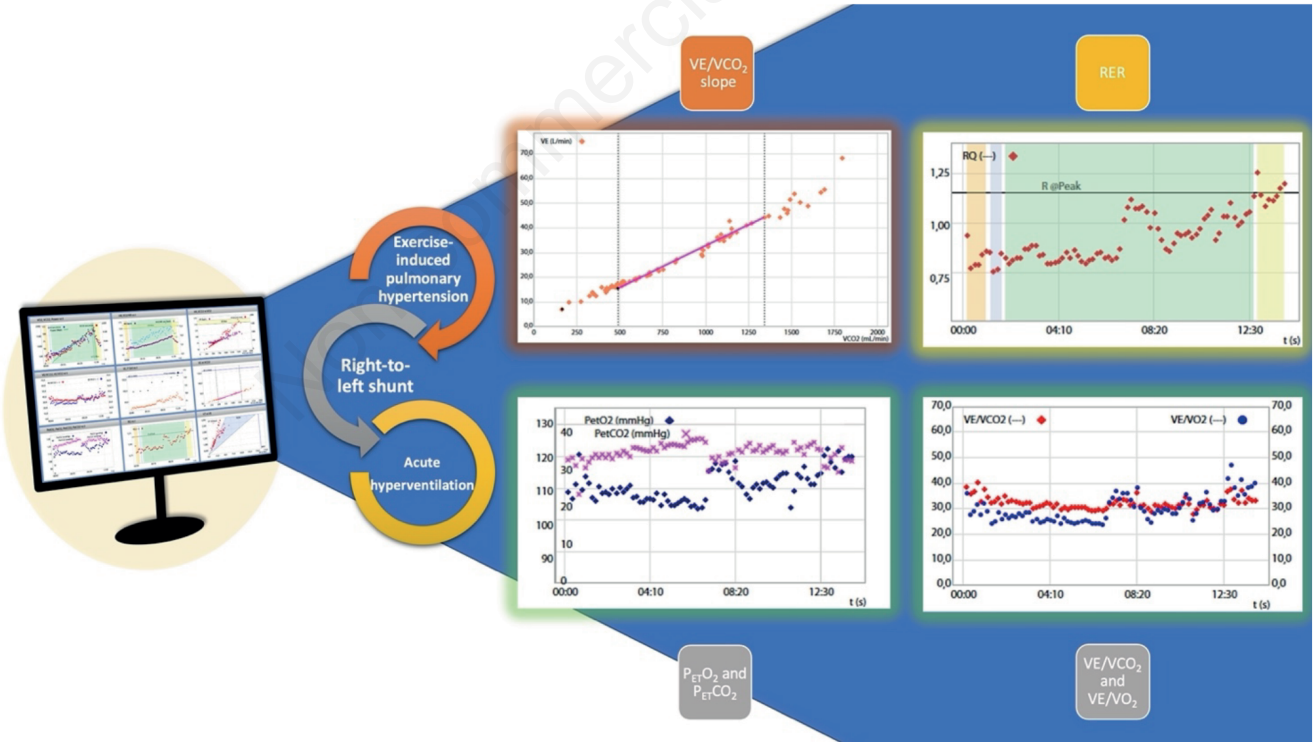
Investigation: cardiopulmonary exercise testing

The test was physician-supervised and conducted on an electromagnetically braked cycle ergometer. Breath-by-breath gas exchange measurements (Quark PFT, Cosmed, Albano Laziale, Italy) and recordings of electrocardiogram, blood pressure, and oxygen saturation (SpO_2) were conducted following the Association for Respiratory Technology and Physiology statement [2]. The test was performed with a 10-watt ramp protocol, calculated through the modified equation of Wasserman [3]. The test was considered normal since the respiratory exchange ratio (RER) at peak exercise was >1.10. As a result, the obtained volume of oxygen consumed per minute (VO_2) peak was severely reduced (*i.e.*, 16.8 ml/kg/min, corresponding to 51% of the predicted value). During exercise, at around 60 WR, a considerable increase in end-tidal oxygen pressure ($P_{ET}O_2$) and RER, with a concomitant decrease in end-tidal carbon dioxide pressure ($P_{ET}CO_2$), and SpO_2, was observed. Concomitantly, an increase in minute ventilation/carbon dioxide production (VE/VCO_2) slope was observed, underlying an exercise-induced PH. Figure 1 represents Wasserman's 9-panel plot (5th edition) and the gas exchange analysis. Table 1 shows the main changes in CPET-derived parameters during exercise in patients with a right-to-left shunt.

Management

In the suspicion of an inter-atrial shunt, we subsequently performed a TTE and transcranial Doppler with bubble test. Both imaging exams showed findings compatible with the presence of a patent foramen ovale (PFO), as seen in Figure 2. Furthermore, a transesophageal echocardiogram (TEE) was carried out to provide a detailed assessment of the defect. According to the definition of Rana *et al*. [4], the PFO at TEE had a "simple" morphology since no atrial septal aneurysm, Eustachian valve, or thickened secondary septum were detected [5]. The PFO was characterized by a tunnel length of 6.5 mm and a single orifice opening into the left atrium of 4.5 mm with no signs of shunt at rest; however, the Valsalva maneuver helped unveil a right-to-left shunt (Figure 2).

Considering the PFO detection with a right-to-left shunt and the history of previous CVA, the percutaneous closure of the defect seemed to be indicated [6]. Nevertheless, we decided not to perform the percutaneous closure of PFO because of a possible hemodynamic worsening considering the concomitant presence of HF; at discharge, the patient was given the indication of long-term antiplatelet therapy with acetylsalicylic acid since the previous episode of CVA.



$P_{ET}CO_2$, end-tidal carbon dioxide pressure; $P_{ET}O_2$, end-tidal oxygen pressure; RER, respiratory exchange ratio; RQ, respiratory quotient; t, time; VE/VCO_2, ventilation/carbon dioxide production; VE/VO_2, ventilatory equivalent for the volume of oxygen consumed per minute; VE, ventilation; V_T, tidal volume.

Figure 1. Cardiopulmonary exercise testing findings with focus on minute ventilation/carbon dioxide production (VE/VCO_2) slope, respiratory equivalents, end-tidal oxygen pressure ($P_{ET}O_2$), end-tidal carbon dioxide pressure ($P_{ET}CO_2$) and respiratory exchange ratio (RER). At 60 WR of exercise, the sudden increase in VE/VCO_2 indicates that the patient experienced exercise-induced pulmonary hypertension, leading to right atrial pressure overcoming left atrial pressure. Subsequently, it was observed a concomitant rapid increase in $P_{ET}O_2$ and RER was observed, with a decrease in $P_{ET}CO_2$. The result is a right-to-left shunt, compensated by a hyperventilation response.

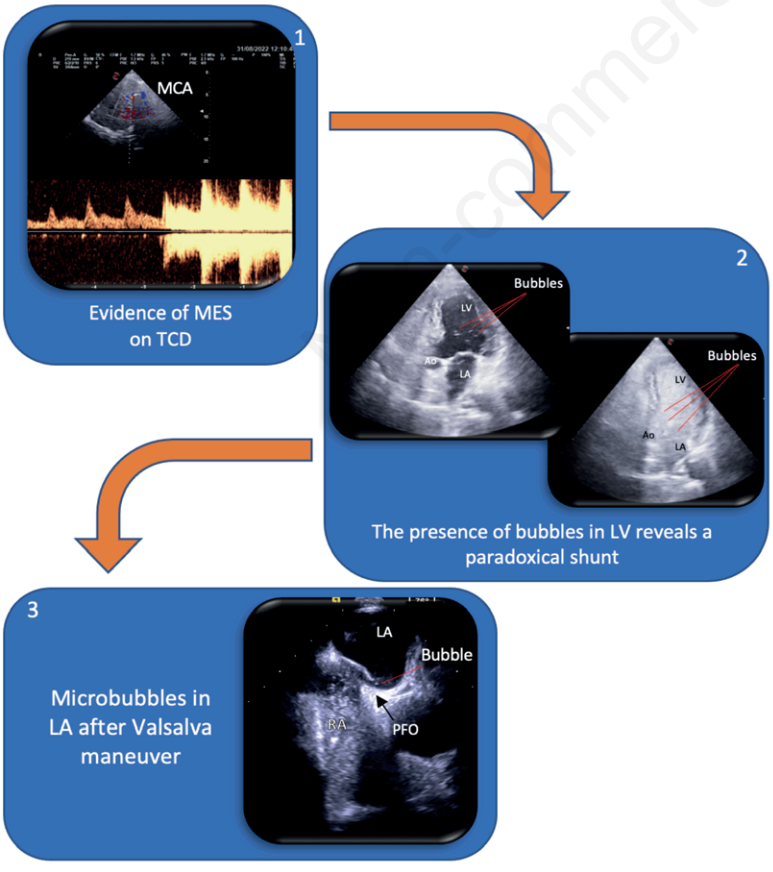
Discussion

The foramen ovale is a vestigial communication between the atria that works as a bypass of the pulmonary circulation during fetal life and then seals at birth after the start of breathing in most people [7]. However, in around 25% of adults, patency of the foramen ovale persists and, in some cases, can lead to a source of a right-to-left shunt, particularly in patients with HF who can experience PH at rest or during exercise [7]. The consequence is a mixture of oxygenated and non-oxygenated blood that affects pulmonary gas exchange efficiency from a long-term perspective [6]. It may also allow blood clots formed in the right circulation to embolize into the left circulation. The most adverse complications of PFO are cerebrovascular events [7].

Table 1. The cardiopulmonary exercise testing-derived parameters in the evaluation of a right-to-left shunt.

Altered parameters in patients with right-to-left shunt during cardiopulmonary exercise testing		
VO_2 max	Diminished	Generally normal in otherwise healthy individuals. In patients with heart failure or pulmonary hypertension is generally diminished.
VE/VCO_2 slope	Augmented	Reflects the onset of pulmonary hypertension and the inefficiency of gas exchange during hyperventilation. Therefore, the intercept value is often deeply diminished and may be negative.
AT	Earlier	Difficult to evaluate in this setting for acute hyperventilation. Generally, present earlier than expected.
VE/VO_2	Augmented	Rapid increase just after the occurrence of a shunt for hyperventilation.
VE/VCO_2	Diminished	Rapid decrease just after the occurrence of a shunt for hyperventilation.
$P_{ET}O_2$	Augmented	Rapid increase just after the occurrence of a shunt for hyperventilation.
$P_{ET}CO_2$	Diminished	Rapid decrease just after the occurrence of a shunt for hyperventilation.
RER	Augmented	Rapid decrease just after the occurrence of a shunt for hyperventilation.
SpO_2	Diminished	The amount of decrease depends on the sizing of the defect.

$P_{ET}O_2$, end-tidal oxygen partial pressure; $P_{ET}CO_2$, end-tidal carbon dioxide partial pressure; RER, respiratory exchange ratio; SpO_2, oxygen saturation; VE/VO_2, ventilatory equivalent for the volume of oxygen consumed per minute; VE/VCO_2, ventilatory equivalent for the volume of carbon dioxide produced per minute; VE/VCO_2 slope, minute ventilation/carbon dioxide production slope; VO_2 max, oxygen consumption.



Ao, aorta; LA, left atrium; LV, left ventricle; MCA, middle cerebral artery; MES, micro-embolic signals; PFO, patent foramen ovale; RA, right atrium; TCD, transcranial doppler ultrasound.

Figure 2. Timeline of imaging diagnostic investigations used in the presented clinical case to diagnose the presence of patent foramen ovale (PFO). 1) The transcranial Doppler ultrasound method uses power M-mode Doppler interrogation of the basal cerebral arteries to detect microbubbles crossed right to the left into the systemic circulation; the study is performed with normal respiration and with the Valsalva manoeuvre. 2) A transthoracic echocardiogram with bubble test can be used for the initial evaluation of PFO; it plays an essential role in the assessment of paradoxical shunt. Several bubbles can be seen in the left cavities. 3) A transoesophageal echocardiogram is required to further characterize the atrial septal abnormalities; thanks to its better image quality, it permits a comprehensive evaluation of PFO and guides in percutaneous closure.

From a pathophysiological point of view, in the presence of a PFO and increased pulmonary vascular resistance, the venous return induced by exercise increases and leads to higher right atrial pressure. When the latter exceeds left atrial pressure, the venous return can shunt through the PFO, diverting deoxygenated, acidemic, CO_2-rich blood to the systemic circulation [8].

Thus, it induces chemoreceptor activation, which, in turn, induces hyperventilation in order to adequately compensate for the high amount of CO_2 in blood coming from the right sections of the heart [9], as evidenced by the gas analysis by a sudden increase in $P_{ET}O_2$ and a decrease in $P_{ET}CO_2$.

Generally, a right-to-left shunt through a PFO or a small atrial septal defect (ASD) is very unlikely since left atrial pressure is generally higher than right atrial pressure [8]. However, in the presence of PH, right atrial pressure can overcome left atrial pressure and force venous blood through the defect directly into the systemic circulation [8].

In the presented case, the concomitant increase in VE/VCO_2 slope underlines an exercise-induced PH, which is frequently associated with HF and further contributes to dyspnea and exercise intolerance [10]. In this case, PH worsened during exercise, determining the inversion of the shunt in a patient with an unknown PFO.

Our observations agree with the criteria postulated in 2002 by Sun *et al*. to prove a right-to-left exercise-induced shunt (EIS) [8]. These criteria included a sudden increase in $P_{ET}O_2$ (with a simultaneous sustained decrease in $P_{ET}CO_2$), an abrupt and sustained increase in the RER, and a decrease in SpO_2. In this study, investigators who interpreted the gas exchange pattern were blinded to the echocardiographic findings. Results demonstrated that 45% of patients had EIS at gas exchange interpretation, and almost all of them were also positive for a PFO by echocardiography. Furthermore, using the resting echocardiography as a reference, the sensitivity, specificity, positive and negative predictive values, and accuracy are all between 90% and 96%, demonstrating the importance of CPET in diagnosing a PFO [8].

In the present case report, TTE did not show signs of an interatrial shunt when performed at rest. In effect, the sensibility of TTE alone in diagnosing PFO at rest is low. In this sense, the Valsalva maneuver is essential for detecting right-to-left shunts when performing TTE. During this maneuver, right atrial pressure rises and overcomes left atrial pressure, allowing more precise detection of the right-to-left shunt [4]. However, even using the Valsalva maneuver, the incidence of PFO in normal subjects is reported at just 5% to 18%. This may happen because the maneuver does not always produce enough blood shunt to change interatrial pressure significantly [11].

It is essential to remember that these changes are not specific to PFO or ASD and are possible in any condition leading to a right-to-left shunt, such as ductus arteriosus or intrapulmonary shunt [3]. Lovering *et al*., using invasive CPET, demonstrated that in healthy subjects, the presence of PFO does not significantly affect pulmonary gas exchange efficiency during maximal exercise [12]. Indeed, they found that the alveolar-to-arterial difference in O_2 tension was significantly higher in PFO patients at rest in conditions of both normoxia and hypoxia but not altered at the peak of exercise in either oxygen condition [12]. Interestingly, PFO patients may also show arterial hypoxemia at the peak of the exercise in normoxia due to a temperature-induced oxygen-hemoglobin dissociation curve. However, as presented in this case, patients with HFrEF and exercise-induced PH present a worse response.

Since there has been a growing interest in interventional procedures for PFO closure, we may wonder if it may be linked to improved exercise capacity in those patients. A study by Yoshiba *et al.* [13] recruited 29 otherwise healthy asymptomatic or mildly symptomatic adult patients after a transcatheter ASD closure using an atrial septal occluder. They performed CPET and found that, although peak VO_2 did not improve 3 months after the closure, a significant improvement was displayed 6 and 12 months after the intervention [13]. They further observed that the AT (anaerobic threshold) and VE/VCO_2 slope did not significantly change 12 months after the ASD closure, suggesting that respiratory function in ASD patients may take longer to normalize after the closure or a certain degree of pulmonary hypertension may persist [13].

To date, pulmonary hemodynamic and systemic complications may differ between ASD and PFO. Consequently, the hemodynamic changes after defect closure may differ. Also, for patients with HF, only a few published studies are available regarding this aspect. Patients affected by HF are more prone to develop an increase in pulmonary pressure during exercise that may favor a possible shunt through a PFO or an ASD [14]. Therefore, further studies are needed to clarify if an induced right-to-left shunt during effort may limit exercise capacity and be associated with an increased risk of systemic embolism.

Actually, clinical guidelines do not foresee the routine use of CPET in assessing PFO [5,7,15]. For these reasons, since PFO evaluation is usually performed in a rest condition, an assessment during exercise might be particularly helpful, as demonstrated in the present case, since it can clearly identify the different components of dyspnea.

Furthermore, we wonder whether the exercise-induced right-to-left shunt may represent a clinical indication of percutaneous closure of the defect since it could potentially provoke severe systemic embolism. This observation seems more likely to develop in patients with PFO characteristics favoring inversion of the shunt during exercise and in patients predisposed to experience effort-induced PH.

In the presented case, considering the PFO detection with a right-to-left shunt and the history of previous CVA, the percutaneous closure of the defect seemed to be indicated [6], since the worsening of PH induced by exercise increases the possibility of paradoxical embolism, especially in the presence of an ICD lead.

However, in this setting of patients, it could be possible that PFO closure may worsen hemodynamics [16,17]. In fact, in the setting of HF, patients are more prone to develop PH during exercise, and the PFO may represent an outlet valve for the left atrial pressure increase during effort [17,18], while the right heart chambers are more compliant to increased afterload. The presence of a PFO can unload the left atrium, and there is evidence that patients with PFO show a lower risk of HF than those without PFO [16].

From a pathophysiological point of view, the left ventricle with impaired systolic function works with increased end-diastolic pressures and also left atrium mean pressure, which in turn can be reduced from a left-to-right shunt that, in this case, may play the role of a small inter-atrial defect. This eventually leads to decreased pulmonary venous pressures and, consequently, lower levels of exercise limitation and dyspnea.

Conclusions

In the presented case, CPET helped diagnose an unknown PFO with a right-to-left shunt induced by effort in a patient with a previous CVA. This observation demonstrates that it could be helpful to identify this condition during exercise and to discern patients with a higher risk of cardiovascular events that would benefit from a percutaneous closure.

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