A patient with pulmonary embolism and patent foramen ovale
The value of transcranial doppler

Isaac Chouris¹,
Maria Stougianni¹,
Antonios Samaras²,
Maria Georgiou¹,
Dimitrios Lagonidis¹

¹Intensive Care Unit,
²Department of Cardiology,
Giannitsa General Hospital, Giannitsa, Greece

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INTRODUCTION

Pulmonary embolism (PE) is a significant complication of orthopedic surgery, although it is rare after arthroscopic surgery. PE is stratified into low, intermediate or high risk, depending on the haemodynamic status of the patient and the presence of markers of right ventricular dysfunction. Both the management and the choice of the appropriate level of care [i.e., intensive care unit (ICU), coronary care unit (CCU), general ward] are dictated by the severity of symptoms and the coexisting risk factors. The hypoxaemia associated with PE is usually due to a low ratio of ventilation and perfusion and consequently it is usually easily corrected with supplemental oxygen.
Refractory hypoxaemia should raise the suspicion of additional oxygenation disorders requiring further investigation. Until recently, assessment of the possible presence of an intracardiac shunt could only be undertaken with the use of cardiac ultrasonography, which required specialized cardiological skills. Newer technological advances, such as the use of transcranial Doppler ultrasonography, provide more convenient methods.

The patient presented in this case report consented to the anonymous publication of the relevant clinical data.

**CASE REPORT**

A 46 year-old male, obese [body mass index (BMI) 35.6] and a heavy smoker, with an unremarkable previous medical history, was admitted to a provincial general hospital for elective arthroscopic surgery due to a meniscus injury of the left knee. Postoperatively, on the afternoon of the day of operation, he had an episode of dyspnoea of sudden onset with hypoxaemia (SpO₂: 87% on atmospheric air) and tachycardia. Based on the clinical situation, and taking into account the Modified Wells Criteria for PE, according to which the patient had a score of 6 points, diagnostic testing for PE was decided upon. The findings of the clinical examination rendered any other aetiology for the hypoxaemia less probable (e.g., pulmonary oedema, fat embolism syndrome). Emergency chest computerized tomography (CT) angiography (Philips Tomoscan AV, spiral CT), showed probable filling defects in segmental branches of the inferior lobes bilaterally. PE was diagnosed and the patient was transferred to the ICU because of severe oxygen-refractory hypoxaemia, mainly due to concern about the appropriate level of monitoring needed, which was not judged feasible in the orthopedics ward and no place was available in the CCU.

On admission to the ICU the patient was fully awake, oriented, afebrile, with a respiratory rate of 25 breaths/min and was haemodynamically stable with mild tachycardia (heart rate: 100/min, blood pressure: 163/82 mmHg) and lung auscultation was unremarkable. Arterial blood gases analysis (on non-rebreathing mask at 10L/min) showed pH=7.398, pCO₂=44.0mmHg, pO₂=76.9mmHg, HCO₃=26.5mmol/L, Sat=97% and he had an APACHE II score of 6.

Transthoracic echocardiography (TTE) examination (Acuson 128XP/10c) showed mild dilatation of both the left and right heart chambers, paradoxical ventricular septal motion, and a nonsignificant pericardial effusion with no other pathological findings. ProBNP<60pg/ml (proBNP, ROCHE), troponine T test (T Quantitive, ROCHE) twice negative, D-dimers: 891ng/ml. The ECG showed sinus tachycardia and the chest X ray revealed bronchovascular prominence and central pulmonary vascular dilatation (Figure 1), while the preoperative chest X ray had been unremarkable.

With a diagnosis of intermediate-risk PE(1) the patient was started on therapeutic anticoagulation, initially with low molecular weight heparin, followed by acenocoumarol (Sintrom) on the third day of his ICU stay. Therapeutic International Normalized Ratio (INR) was achieved on the fifth day.

TTE was repeated on the third day in ICU, demonstrating adequate heart contractility (Ejection Fraction 73%) and low grade aortic valve and pulmonary valve regurgitation, with no signs of paradoxical ventricular septum motion.

From the third through the sixth day of his ICU stay, the patient remained hypoxic with continuously increased needs for supplementary oxygen (non-rebreathing oxygen mask at a flow of 10-15L/min), and showed no signs of respiratory improvement, maintaining SpO₂ 96-98%. In addition, repeated brief (lasting a few minutes) episodes of desaturation were noted, presenting with severe dyspnoea, the SpO₂ falling as low as 85%, with poor response to oxygen flow increase and markedly slow improvement of hypoxia. These daily manifestations of hypoxaemia, always coinciding with effort related to defaecation or

![FIGURE 1](image-url). 46 year-old male with pulmonary embolism: Supine chest X ray, on ICU admission, demonstrating prominent bronchovascular network and dilatation of the central pulmonary vessels.
urination and accompanied by intense respiratory distress, led to prolongation of his ICU stay, once again because of an insufficient level of monitoring elsewhere. This further deterioration of the refractory hypoxia, triggered by the intense Valsalva manoeuvres performed by the patient in these instances, raised the suspicion of a coexisting transient intracardiac (intraatrial) shunt mechanism (right-to-left). Valsalva manoeuvre attempts performed at medical request (in semi-recumbent position) failed to reproduce significant desaturation, probably because of inadequate cooperation on the part of the patient. It must be stressed that there was no comparative SpO₂ measurement with the patient either in the sitting or supine position.

Referral of the patient to a tertiary hospital was deemed necessary, for investigation of the probability of a patent foramen ovale (PFO) or atrial septal defect (ASD) – while the presence of intrapulmonary shunt as a cause of hypoxaemia (atelectasis, pneumonia, pulmonary oedema, pulmonary infarct) was considered less probable, based on the imaging findings. At that time no cardiac ultrasound operator was available in the hospital with acceptable experience in TTE with bubble testing.

The patient underwent a transcranial Doppler (TCD) bubble study, following the international Consensus Meeting recommended protocol for the detection of right-to-left shunt with the administration of the microbubble contrast agent 5 seconds before performing the Valsalva manoeuvre for 10 seconds (once only) and observing for 20 seconds. The study yielded positive results for the presence of interatrial communication or PFO and was classified as grade II to III (Spencer PFO grading scale) (Figures 2a, 2b). It should be noted that the patient declined transoesophageal echocardiography (TEE, which was the test of choice, only consenting to TCD.

On the eighth day the patient's condition was improved; the need for supplemental oxygen was substantially reduced (arterial blood gases: pH=7.41, pCO₂=41.9mmHg, pO₂=76.5mmHg, HCO₃=26.0mmol/L, SpO₂ 94-96%, on nasal cannula with oxygen flow at 6L/min), allowing discharge from the ICU to the medical ward. Referral for pulmonological assessment was arranged, along with further cardiological investigation aimed at reaching a precise diagnosis of the type of ASD and to estimating the severity and the need for treatment. The recommended, indispensable follow-up with TEE was postponed due to the patient’s initial refusal, but after thorough explanation and reassurance the bubble-test TEE was performed (General Electric Vivid E9, multiplane probe) two months after discharge from ICU, and this demonstrated the presence of PFO, ruling out other types of cardiac pathology. At the time of examination, the right-to-left shunt not severe, and in view of the passage of two months since the PE, two key elements needed to be taken into account: a) the clinical improvement, and b) the fact that no signs of pulmonary arterial hypertension were recorded during the TEE that might worsen the shunt.

FIGURE 2: Transcranial Doppler (TCD) bubble-test study in 46 year-old male. 2A: TCD bubble-test study, spontaneous breathing without Valsalva manoeuvre; only occasional high intensity signals (HITS) are recorded, which reflects the scarce presence of bubbles in the middle cerebral artery.

FIGURE 2b: TCD bubble-test study during Valsalva manoeuvre. Presence of bubbles manifested as high intensity signals (HITS) in the middle cerebral artery, consistent with patent foramen ovale (PFO).
PFO constitutes a form of interatrial communication which is a remnant of the embryonic life. Specifically, it is an anatomical abnormality of the heart where the normal closure of the opening between the atrial septum primum and the septum secundum at the location of fossa ovalis has not fully taken place. Under certain circumstances, this allows a right to left intracardiac communication (shunt) at the atrial level. Most patients with PFO are asymptomatic, but some may present with stroke or transient ischaemic cerebral attacks\(^2,4\) or even migraine\(^5\). The prevalence of PFO in the general population is estimated to be around 25-30\(^\%\)\(^6\), which warrants a high index of suspicion, particularly in a critically ill patient presenting with refractory hypoxaemia and disproportionately mild X ray findings (not indicative of a serious pulmonary parenchymal disorder), or in the case of paradoxical embolism, when the embolic material enters the arterial circulation through the intracardiac communication defect.

Any situation raising the pressure in the right heart chambers and simultaneously altering the pressure gradient between the atra may open the foramen ovale, creating intracardiac shunt conditions. Situations inducing pulmonary hypertension and cor pulmonale are frequent in patients in critical care, especially in those with pulmonary embolism or acute respiratory distress syndrome (ARDS), or even as a result of the use of positive pressure mechanical ventilation\(^7,8\). All these situations commonly lead to worsening of the already established hypoxaemia. A study of 203 patients in critical care with ARDS demonstrated that patients with coexisting PFO had a poor response in terms of oxygenation to the application of positive end-expiratory pressures (PEEP), showing a considerably greater need for implementation of adjuvant therapeutic interventions, such as prone positioning and use of nitric oxide (NO), and they required a longer stay in the ICU\(^9\).

An observational prospective study in 139 consecutive patients with PE and PFO demonstrated that they are at greater risk for paradoxical embolic events (cerebral vascular stroke or peripheral arterial embolism) and exhibit higher rates of mortality from these conditions than patients without PFO. Overall, the presence of PFO signified a 5.2 times greater risk of a complicated clinical in-hospital course\(^10\). Another study of patients with PE with haemodynamic instability, indicated that patients with PFO had a significantly higher frequency of cardiopulmonary complications, such as increased need for use of catecholamines, intubation and mechanical ventilation\(^11\).

Patients with PE complicated by paradoxical embolism are recommended to undergo a thorough investigation in order to confirm the possible presence of interatrial communication, to assess the risk of recurrence and to consider referral for PFO closure\(^12\). Understanding the pathophysiological mechanisms

**FIGURE 3A**: TEE (50º angle) showing both atria and the atrial septum before the bubble-test study.

**FIGURE 3B**: TEE (50º angle), bubble-test study during Valsalva manoeuvre: right atrium swelling with bubbles, at the same time detection of the presence of bubbles in the left atrium, thus establishing the presence of patent foramen ovale (PFO). The communication is depicted in the central part of the atrial septum.

DISCUSSION

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has not fully taken place. Under certain circumstances, this allows a right to left intracardiac communication (shunt) at the atrial level. Most patients with PFO are asymptomatic, but some may present with stroke or transient ischaemic cerebral attacks\(^2,4\) or even migraine\(^5\). The prevalence of PFO in the general population is estimated to be around 25-30\(^\%\)\(^6\), which warrants a high index of suspicion, particularly in a critically ill patient presenting with refractory hypoxaemia and disproportionately mild X ray findings (not indicative of a serious pulmonary parenchymal disorder), or in the case of paradoxical embolism, when the embolic material enters the arterial circulation through the intracardiac communication defect.

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leading to hypoxaemia is of considerable assistance in the management of incidents of acute severe desaturation that may arise, as in the case of the patient presented here. The pressure increase in the right heart chambers - albeit transient, as in the Valsalva manoeuvre - leads to opening of the PFO and, eventually, to an intracardiac shunt. This, in turn, decreases the oxygen saturation of mixed venous blood and induces hypoxaemic pulmonary vasoconstriction thus worsening further the pressure in the right heart chambers \[13\]. This chain of events results in a "vicious circle" that tends to sustain the shunting effect. It is of note that positive pressure respiratory support may worsen this hypoxaemia, since the increase of the intrathoracic pressure is in itself capable of causing opening of the foramen ovale, particularly when high levels of PEEP are applied \[14\].

Hypoxaemia in patients with PE is usually not refractory to oxygen administration, apart from massive PE presenting with severe ventilation/perfusion mismatch. The presence of refractory hypoxaemia in these situations should raise the suspicion of the presence of alternative or complementary causes contributing to hypoxaemia, including shunting mechanisms (intrapulmonary or intracardiac). In this situation PFO constitutes a highly probable explanation, considering its significant prevalence in the general population (20-30%).

Excluding PFO, the right-to-left shunt at heart level might be caused by an ASD, which is the most common congenital cardiac disorder, encountered in approximately 1‰ of the healthy population, and accounting for 25-30% of the congenital heart diseases diagnosed in adults \[15\]. The additional load that burdens the right heart chambers may be adequately compensated for many years before manifesting any serious symptoms, but in advanced stages, when reactive pulmonary hypertension ensues, a right-to-left shunt is established. This is also observed in situations causing acute strain of the right heart (PE, acute myocardial infarction leading to right heart insufficiency, ARDS, severe tricuspid regurgitation) \[13\].

In order to establish the diagnosis of PFO, ultrasonographic cardiological assessment is required. Bedside TTE may, in some cases, identify the disorder. However, the use of TEE has been shown to be more sensitive and has significantly improved the diagnostic accuracy in PFO \[16\]. The saline contrast study, called "bubble test" (the injection of a shaken normal saline solution that contains tiny bubbles into one of the larger veins or the right atrium) is superior in demonstrating PFO to the color visualization of blood flow using Doppler technique. The test is performed before and after Valsalva manoeuvre, which in many cases is indispensable for the opening and thereby the demonstration of a PFO \[7\]. Limitation of the TEE technique are that it is a semi-invasive method and that it depends to a great extent on good patient cooperation for achieving an effective Valsalva manoeuvre.

The most recent method recommended for identifying PFO is TCD \[17,18\], the advantages of which are that it is cheaper and faster than TEE, but comparable with TEE in specificity and sensitivity, and the patient’s cooperation is easier \[17,18\]. The bubble test is considered positive when bubbles that have passed through the foramen ovale are detected in the cerebral arteries. As for the TEE method, the Valsalva manoeuvre is also applied for TCD, in hope of achieving the conditions required for the opening of the foramen ovale. The TCD bubble study is not capable of estimating the size of the opening between the atria, although, in theory, it may be of assistance in assessing approximately how much embolic material may pass from the venous circulation to the cerebral arteries.

Use of the saline contrast study (bubble test) is not only safe, but also provides an immediate answer to the question of whether or not there is intra-atrial communication in a given patient \[19\]. It is important not to overlook the major advantage of TEE, which is that it enables recognition of the type of intra-atrial communication, and specify whether it is PFO or another kind of ASD \[20\].

In the case presented here, the TCD method was chosen for diagnosis of a possible PFO because of the relatively minimal cooperation required (the patient initially refused to undergo TEE). For this specific patient complementary follow-up with TEE was imperative for reasons of differential diagnosis.

In conclusion, a high index of suspicion of PFO is recommended in refractory hypoxaemia that is unexplained by other causes, particularly under conditions favouring the increase of pressure in the right heart chambers (PE, mechanical ventilation) and right-to-left shunting. The TCD method is proposed as an initial step in the diagnostic process for PFO, as it is cheaper, faster to perform and comparable with TEE in terms of sensitivity and specificity.

The evolution of medical technology extending to all aspects of everyday clinical routine, with the introduction of reliable, user-friendly, portable ultrasonographic devices, in combination with the safety of the bubble test, renders the application of these techniques simpler and more accessible for clinicians, adding another weapon in their diagnostic arsenal.
REFERENCES