Hemidiaphragmatic paralysis: An underestimated etiology of right-to-left shunt through patent foramen ovale?

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Abstract
Objective: To report a specific pathophysiology of hemidiaphragmatic paralysis that may result in severe hypoxemia.
Design: Case series.
Setting: Intensive care unit in a cardiology hospital.
Patients: The series included three patients with refractory hypoxemia in whom a diagnosis of right-to-left-shunt through a patent foramen ovale was made by contrast echocardiography. The three patients had a complete right hemidiaphragmatic paralysis.
Intervention: Permanent percutaneous closure of the patent foramen ovale was successfully proceeded in all cases.
Main result: These procedures resulted in complete normalization of arterial oxygen saturation.
Conclusion: To our knowledge, only three previous reports have described the association of right-to-left shunt through a patent foramen ovale and hemidiaphragmatic paralysis. Such association may be underestimated.

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Keywords
Right-to-left shunt; Patent foramen ovale; Hemidiaphragmatic paralysis

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Foramen ovale (FO) is a remnant of a flap between the septum primum and secundum allowing fetal right atrial blood to pass into the left atrium. Besides the risk of embolism, patent foramen ovale (PFO) may generate a right-to-left shunt (RTLS) with elevated or normal right cardiac pressures. In this case, the shunt will increase dyspnea and will cause refractory hypoxemia. Partial or complete pneumonectomy is a well-known etiology of RTLS, secondary to the reopening of the FO. However, isolated diaphragmatic dysfunction has also been associated with intracardiac RTLS through PFO. To our knowledge only three earlier reports have described such association.

In the present paper, we report three new patients with hemidiaphragmatic paralysis who were diagnosed RTLS through a PFO.

**Case 1**

A 79-year-old woman was admitted in the intensive care unit for a progressive dyspnea, increasing fatigue and general discomfort for three weeks, without any chest pain. Her medical history was unremarkable. At admission, physical examination revealed a respiratory rate of 22/min with an oxygen saturation of 84% on room air. Lungs were clear. ECG was normal. The arterial blood gas analysis is shown in Table 1. D-dimers level reached to 2014 ng/ml (N ≤ 500 ng/ml). A bilateral venous thrombosis was diagnosed by venous ultrasonography. Chest X-ray revealed an elevated right hemidiaphragm, with normal parenchyma (Fig. 3b). Transthoracic echocardiography showed a normal left ventricular ejection fraction, without any valvular disease and a normal right ventricle. Systolic pulmonary artery pressure was measured at 28 mmHg. A small pulmonary embolism was confirmed by a spiral CT-scan showing a left lingular artery thrombosis with an avascular triangular pulmonary image of pulmonary infarction.

Despite effective anticoagulant therapy for one week, the patient remained breathless. Hypoxemia appeared disproportionate in regard to the small pulmonary embolism. Contrast transesophageal echocardiography with 10 mL agitated saline solution rapidly injected into a peripheral vein, revealed an RTLS through a PFO (Figs. 1a and 2a). It was associated with an atrial septal aneurysm, defined by a phasic excursion of the interatrial septum during the cardiorespiratory cycle more than 15 mm in total amplitude (Fig. 1a). Permanent closure of the PFO by a double-umbrella (Amplatzer, 35 mm) device deployed using a standard technique of cardiac catheterization was proceeded three weeks after her admission (Fig. 3a). Immediately before closure of the PFO, catheterization confirmed the absence of right-to-left pressure gradient. Specifically, the mean left atrial pressure was measured at 8 mmHg, the mean right atrial pressure was 4 mmHg and the systolic and diastolic right ventricular pressures were 20 and 0 mmHg, respectively. In addition, left atrial oxygen saturation reached 65% but 95% in the left superior pulmonary vein after closure of PFO. The procedure resulted in a marked and immediate improvement of oxygen saturation, giving the opportunity to withdraw oxygen. The arterial gas analysis after procedure is shown in Table 1. In addition, during the procedure, cinefilm confirmed a right hemidiaphragmatic paralysis. A cancer of the pancreas associated with liver metastasis and a huge enlargement of the liver were diagnosed three weeks later in this patient.

**Case 2**

A 61-year-old woman was hospitalized for recurrent inferior myocardial infarction. Her medical history showed a first inferior myocardial infarction four months earlier treated by primary percutaneous transluminal coronary angioplasty with stenting on distal right coronary artery. A double coronary artery bypass on left anterior descending artery and marginal branch was performed two months later to achieve complete revascularisation. At admission, physical examination was unremarkable. ECG revealed ST-elevation in inferior

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Arterial blood gas analyses of the three patients, before and after permanent closure procedures of PFO</th>
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<tbody>
<tr>
<td></td>
<td>Patient 1</td>
</tr>
<tr>
<td></td>
<td>Before</td>
</tr>
<tr>
<td>pH</td>
<td>7.47</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>60</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>30</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>84.2</td>
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leads and normal repolarization in right leads. Chest X-ray showed an elevated diaphragmatic right cupola, resulting from a phrenic nerve injury during surgery (Fig. 3c). Reperfusion was achieved by emergent primary percutaneous transluminal coronary angioplasty on the distal right coronary artery. At admission, we noticed a refractory hypoxemia, still present during hospitalization. Table 1 shows the results of the arterial blood gas analysis. Transthoracic echocardiography showed a left ventricular ejection fraction of 50% with inferior akinesia, and normal right ventricular function. A small mitral regurgitation was noticed. Contrast transesophageal echocardiography showed an atrial septal aneurysm, and an RTLS through a PFO (Figs. 1b and 2b). Permanent closure of the PFO by a double-umbrella (Amplazer, 25 mm) device was proceeded, 15 days after her admission. Catheterization gave no evidence of right-to-left pressure gradient, as both mean left and right atrial pressures reached 5 mmHg before permanent closure of the PFO. Systolic and diastolic right ventricular pressures were, respectively, 29 and 0 mmHg. This procedure resulted in immediate and complete normalization of oxygenation saturation. The arterial blood gas analysis on room air after procedure is shown in Table 1.

Case 3

An 84-year-old woman was admitted in intensive care unit for a progressive dyspnea for three weeks. Her medical history showed a stroke three years ago. At admission, physical examination revealed dyspnea with an oxygen saturation of 95% with oxygen at 3 L/min. The arterial blood gas analysis on room air is shown in Table 1. D-dimers level reached to 829 ng/mL (N < 500 ng/mL). ECG was normal. Chest X-ray revealed an isolated elevated right hemidiaphragm (Fig. 3d). Venous ultrasonography was normal. Transthoracic echocardiography was normal without elevated systolic pulmonary artery pressure or right ventricle dysfunction. An atrial septum aneurysm was
noticed. Spiral CT-scan showed distal and unilateral pulmonary embolisms. Transesophageal echocardiography revealed a massive RTLS through PFO by bubble contrast (Fig. 2c) and confirms atrial septum aneurysm (Fig. 1c). Permanent closure of the PFO was proceeded. During catheterism, simultaneous right and left atrial pressures were measured (Fig. 4). At some time of the cycle, left atrial pressure became lower than right atrial pressure. Systolic and diastolic right ventricular pressures were 21 and 2 mmHg, respectively.

Discussion

Cumulative data from clinical investigations in more than 1000 patients have demonstrated a 9.3% incidence of PFO by transthoracic echocardiography and 9.2–11.2% by transesophageal echocardiography.\(^6\,7\) In contrast, the autopsy incidence of PFO by probe patency has been reported to be 27.3%.\(^8\)

RTLS through PFO may be associated with low atrial oxygen saturation in case of elevated right cardiac pressure as in such severe pulmonary embolism or Eisenmenger’s syndrome. However, hypoxemia induced by RTLS through PFO may be observed in the absence of elevated right cardiac pressure.\(^9\) Partial or complete right pneumonectomy is the most frequent cause of reopening of the FO.\(^1\,10\,11\) Only few cases have been described with left pneumonectomy.\(^12\) Mediastinal shift following right lung resection has been suggested to alter the relative position of the atrial septum and the inferior vena cava, directing the blood flow through the septal defect. An important right cupola elevation secondary to diaphragmatic paralysis as in our cases could be compared to a right partial pneumonectomy.\(^12\)

In the present paper, we report three new cases of RTLS through a PFO causing refractory hypoxemia, associated with a right diaphragmatic dysfunction. Only three similar cases have been previously described in literature. In the first three cases, there was a right isolated hemidiaphragmatic dysfunction, without any elevated right cardiac pressure.\(^2\,4\) This was also the case of our three patients. In the first and third cases, pulmonary embolism were too small to produce a rise in the pulmonary artery pressure. In addition,

Figure 2  The right-to-left shunt from right atrium to left atrium is well shown after echocontrast injection in basal short axis transesophageal 90-degree plane in patient 1 (a) and 60-degree plane in patients 2 (b) and 3 (c).
shunting persisted despite an efficient anticoagulation treatment and catheterization confirmed that there was no evidence of right-to-left mean pressure gradient. Catheterism measurements showed that the left atrial pressure was most of the time superior to right atrial pressure. But, at some time of the cardiac cycle (systolic phases), left atrial pressure became briefly lower than right atrial pressure, without elevated right pressure. This could contribute to the RTLS, but cannot alone explain the syndrome. The PFO allows more streaming of venous blood from inferior venous cava through the defect. This redistribution of flow caused by an anatomic distortion of the right atrium or the atrial septum, secondary to hemidiaphragmatic paralysis, could contribute to the RTLS. In addition, we cannot exclude formally that the coronary event in case 2 or the thromboembolic events may have triggered the RTLS at some point in the setting of right diaphragmatic paralysis.

In our cases, we have not found any evident platypnea—orthodeoxia syndrome. However, we observed a further transitory decrease in oxygen saturation when the patient sat up in both cases. Such syndrome is also inconstantly observed in references.

In our cases, an atrial septal aneurysm was associated with the PFO, as in the previous cases reported, the presence of atrial septal aneurysm was not precised. The presence of atrial septal aneurysm has been demonstrated to be a predictor of the presence of PFO (OR = 4.57, 2.18–9.57).
However, we cannot conclude that this association is necessary to produce a right-to-left shunt without elevation of right filling pressure.

For our three cases, there has been an immediate therapeutic implication. Percutaneous catheter closure of the PFO was performed with immediate improvement in symptoms and in oxygen saturation. This has already been described by Ghamande et al. with normalization of oxygen saturation. In another case, Cordero et al. reported the normalization of PaO₂ and of the shunt fraction when the hemidiaphragmatic paralysis spontaneously resolved. This last observation demonstrates formally that elevated hemidiaphragm alone favoured the RTLS through PFO.

In conclusion, the observation of an isolated hemidiaphragmatic paralysis especially on the right side associated with a refractory hypoxemia should lead to perform a contrast echocardiography to search for an RTLS through PFO. Such diagnostic procedure is accompanied by an immediate therapeutic implication.

References