CLINICAL RESEARCH

Should we close hypoxaemic patent foramen ovale and interatrial shunts on a systematic basis?

Faut-il fermer systématiquement tous les foramen ovale perméable et shunt interauriculaires hypoxémiant?

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Patent foramen ovale; Hypoxaemia; Interventional closure

Summary

Background. — Rarely, hypoxaemia is associated with shunt reversal at the atrial level. Closure by interventional catheterization is the treatment of choice but indications and results have been studied insufficiently.

Purpose. — To describe our experience with interventional closure of atrial right-to-left shunts described as hypoxaemic and the impact on patient oxygenation and clinical status.

Method. — Retrospective study in two referral centres, including all patients undergoing closure of interatrial right-to-left shunt associated with hypoxaemia.

Results. — Since 2001, 21 consecutive patients underwent interventional shunt closure using the “Amplatzer® device”; two patients had atrial septal defect and 19 had patent foramen ovale. Three patients had minor adverse events; two patients have a tiny residual shunt. Transcutaneous oxygen saturation and partial oxygen pressure increased significantly from 86 ± 5 to 95 ± 3% (p < 0.001) and from 49.8 ± 6.8 to 82.9 ± 30.4 mmHg (p = 0.001), respectively. Seventeen (80%) patients reported clinical improvement. However, patients with chronic respiratory....
insufficiency remained more symptomatic, with three deaths after a median follow-up of 35 (6–97) months and 89% remaining in New York Heart Association class III/IV (vs 29% of patients without chronic respiratory insufficiency; \( p = 0.035 \)).

**Conclusion.**—Hypoxaemic shunts are treated effectively by transcatheter closure, resulting in functional improvement in patients without respiratory insufficiency. When associated with chronic respiratory insufficiency, hypoxaemia often persists after shunt closure. In such cases, the right-to-left atrial shunt does not seem to be the main cause of hypoxaemia and the indication for closure is questionable.

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control was carried out systematically 1 month after closure, to search for a residual shunt by colour Doppler and contrast injection.

Cardiac catheterization

The transcatheter PFO closure was performed under local anaesthesia or mild sedation after puncture of the right femoral vein and placement of an 8 French sheath. All patients were anticoagulated with unfractionated heparin (100 IU/kg to a maximum of 5000 IU). Anticoagulation was continued for 12 h, then replaced by antiplatelet treatment for 6 months. A balloon occlusion test was performed in nine of our 10 first patients, then it was decided to do it only in the setting of elevated right atrial pressure (>20 mmHg), which was not encountered in the subsequent cases. The devices used for shunt closure were an Amplatzer (AGA Medical, Golden Valley, MN, USA) 25 mm PFO occluder (n = 6), an Amplatzer 35 mm PFO occluder (n = 13), and Amplatzer 20 mm and 26 mm septal occluders for the two ASDs. The devices were implanted according to the method described previously [7]. The procedure, performed under fluoroscopy, was guided by transoesophageal, transthoracic or intracardiac echocardiography with the AcuNav® system (Acunav Diagnostic Ultrasound Catheter, CA, USA) [9]. SaO2 and PaO2 were measured before and 24 h after closing the shunt under initial measurement conditions.

Statistical analysis values are expressed as means ± standard deviations or medians (ranges) when appropriate. Patients were grouped according to the presence or absence of respiratory insufficiency. Statistical analysis was performed using with Microsoft Excel software, version 2007 (Microsoft Corp., Seattle, WA, USA) and JMP version 7.0 (SAS Institute, Cary, NC, USA). Patients with respiratory insufficiency were compared with other patients using the Mann-Whitney and Wilcoxon tests. A p-value < 0.05 was considered significant.

Results

Twenty-one patients (11 men) underwent transcatheter PFO closure (n = 19) or ASD (n = 2) closure for hypoxaemia associated with a right-to-left atrial shunt (Table 1). The patients were diagnosed at a mean age of 65.5 ± 9.8 years. In five patients, the PFO was associated with an aneurysm of the interatrial septum. The patients experienced dyspnoea at minimal exertion (n = 13) or orthopnoea in 33% of cases (n = 8), necessitating transient or continuous oxygen supplement in all cases. Nine (43%) patients had chronic respiratory insufficiency, including obstructive bronchopulmonary disease (n = 5), pneumoconiosis (n = 2), interstitial pulmonary disease (n = 1) and chronic pulmonary thromboembolic disease (n = 1). Two patients had mild pulmonary hypertension (systolic pulmonary artery pressure of 55 mmHg). Two patients had a history of pneumonectomy, whereas one had an aneurysm of the ascending aorta. Four patients had polycythaemia (17–18 g/dL). The hypoxaemia was severe in all patients, with a mean SaO2 of 86 ± 5%. The PaO2 confirmed dyspnoea with 62% in NYHA class III and 38% in NYHA class IV. Two women with an ASD had their transcatheter closure at 73 and 69 years and were in NYHA class III and IV, respectively; their PaO2 measurements were 53 and 43 mmHg, respectively. Their coronary angiograms were normal and right heart catheterization confirmed normal pulmonary artery pressure with systolic pulmonary artery pressures of 35 and 30 mmHg, respectively.

Transcatheter closure was achieved in all patients. Three (14%) minor complications occurred: a transient atrial flutter that resolved spontaneously and two groin haematomas. The mean SaO2 rose from 86 ± 5 to 95 ± 3% (p < 0.001). The mean PaO2 rose from 49.8 ± 6.8 to 82.9 ± 30.4 mmHg (p = 0.001). The difference in PaO2 (∆PaO2) before and after closure was significantly higher in the group of patients who did not have CRI: +45 (16–91) versus +8 (4–36) mmHg in patients with CRI (p = 0.039) (Fig. 1). Transoesophageal echocardiography control 1 month after PFO closure showed a minimal residual interatrial shunt in two (9.5%) patients without residual hypoxaemia. One month after the procedure, dyspnoea had improved in 17 (80%) patients.

After a median follow-up of 35 (6–97) months, three patients in the CRI group had died from their associated comorbidities (two from terminal respiratory insufficiency and the third from lung cancer); there were no reported embolic events and CRI patients were more symptomatic.

### Table 1 Population characteristics before closure of interatrial shunt.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± standard deviation</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>65.4 ± 9.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.0 ± 19.3</td>
</tr>
<tr>
<td>Systolic pulmonary artery pressure (mmHg)</td>
<td>32.0 ± 9.4</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>14.6 ± 2.3</td>
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<tr>
<td>Haematocrit (%)</td>
<td>45.9 ± 6.6</td>
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</tbody>
</table>

![Figure 1. Difference in partial oxygen arterial pressure (ΔPaO2) after right-to-left interatrial shunt closure in patients with chronic respiratory insufficiency (CRI) and those without CRI (N).](image)
with 89% in NYHA class III or IV (whereas only 29% of non-CRI patients were in NYHA class III or IV; \( p = 0.035 \)) (Fig. 2).

**Discussion**

Hypoxaemic interatrial shunts are reported rarely and may be underestimated and underdiagnosed. Our series included cases similar to previously reported studies [3,6—8]. Men and women seem to be affected equally, and the age at diagnosis is rather late:

* 44—79 years in our study;
* 59—78 years for Godart et al. [3];
* 56—78 years for Guerin et al. [6];
* 52—64 years for Seward et al. [10].

The clinical profile was also quite similar to that found in previous studies.

In our study, only two (9%) patients had mild pulmonary hypertension. This is in agreement with the study by Godart et al., investigating the possibility of right-to-left shunt in the absence of elevated pulmonary artery pressure [3]. In this patient population, the direction of the shunt at the atrial level depends highly on the relaxation and compliance of the two ventricles during diastole. Reduced diastolic function of the right ventricle with elevated end-diastolic pressure was the primary cause of right-to-left atrial shunt in a recent study [11]. Hence, patients with pulmonary hypertension will shunt right-to-left at the atrial level only when the right ventricle becomes hypertrophied, and eventually dilated, with reduced diastolic function [3,11,12]. This is likely to be the main hypothesis to explain the right-to-left atrial shunt in the two patients with an ASD in our study. In the setting of a PFO, three additional hypotheses are currently advanced, besides the ratio of filling pressure between the two ventricles. Firstly, modification of the geometry of intracardiac structures after pneumonectomy or dilatation of the ascending aorta results in rocking of the interatrial septum towards the orifice of the inferior vena cava and then promotes a right-to-left shunt [5]. This mechanism can be exacerbated by an exuberant eustachian valve [3]. Secondly, the presence of a paroxysmal right atrium-to-left atrial gradient [3]. Thirdly, hypoxaemia might also be related to extrinsic compression of the right atrium, especially in the upright position, causing an increase in pressures in the right side of the heart. Depending on the underlying disorders, the compression may be the result of a right hydrothorax or a localized pericardial effusion. Compression of the right atrium by a right hydrothorax may play a role after right-sided pneumonectomy [13].

Such assumptions have not been studied precisely in our series, although we found a significant proportion of patients with pneumonectomy (10%) or ascending aorta aneurysm (5%). Careful analysis of a computed tomography scan may help to better elucidate the link between right-to-left atrial shunt and modification of the geometry of the intracardiac structure and/or extrinsic compression of the right atrium.

In our present study, we found a significant proportion (43%) of patients with CRI. Whereas the PFO closure seemed to be highly effective in our patients, with most (80%) showing improvement in oxygenation variables, such improvement was not observed in the CRI patients, who were still dyspnoeic, and most remained in NYHA class III or IV. We hypothesize that the hypoxaemia in CRI patients occurs predominantly through an intrapulmonary shunt associated with their respiratory illness. Although a right-to-left shunt is often associated with CRI due to associated acquired anatomic factors (such as pneumonectomy), its participation in the patient’s hypoxaemia seems to be relatively minor. Unfortunately, transoesophageal echocardiography as a diagnostic tool cannot quantify precisely the part of the hypoxaemia that is due to the extrapulmonary shunt related to the PFO or ASD, compared with the intrapulmonary shunt caused by the CRI. Another interesting method of investigation, in theory, is respiratory function testing. However, this test has produced disappointing results in our experience. In CRI patients, PFO closure only reverses the hypoxaemia partially and obviously does not prevent the potentially fatal outcome of the respiratory disease, as illustrated by the three deaths in our study. Based on our study findings, the indication for PFO closure in CRI patients remains controversial.

All our study patients were in NYHA class III or IV before shunt closure vs 44.8% in the series of Guerin et al. [6]. This advancing NYHA grade with profound cyanosis at rest reflects a profoundly debilitating general condition. Consequently, most of our study patients were likely to be unable to perform any functional assessment, such as a 6-min walking test, appropriately. Moreover, the result of such testing would not modify the indication for PFO closure. In addition, 16/21 of the patients were referred to our department by pneumonologists for urgent or semi-urgent PFO closure. Finally, we had nearly 38% of patients with platypnoea-orthodeoxia syndrome, and interpretation of a 6-min walking test in patients who experience upright hypoxaemia would be difficult.

From a technical point of view, percutaneous closure was achieved in all patients, which corresponds to data from the literature suggesting an effective closure rate of 95—100% [3,6—8,14]. In our study, few (14%) patients experienced complications during transcatheter closure; these complications were minor, in the form of transient supraventricular arrhythmias (atrial fibrillation and flutter) and groin haematomas. However, more serious adverse events may occur. One cerebrovascular accident that resolved within 1 month after closure was reported in by Godart et al. [3]. Regarding the efficiency of the procedure, our small residual
Hypoxemic patent foramen ovale closure

The shunt rate of 9.5% is similar to the 6% reported by Guerin et al. [6]. Godart et al., Rao et al. and Delgado et al. reported higher minor residual shunt rates without the need for re-intervention: 9% [3], 50% [7] and 16% [15], respectively. In the study by Guerin et al., one patient with a significant residual shunt needed the implantation of a second device [6].

Conclusion

Hypoxaemic shunts are treated effectively by transcatheter closure. Their closure is often associated with functional improvement and amelioration of the hypoxaemia, except in CRI patients. In such cases, the right-to-left atrial shunt does not seem to be the main cause of the hypoxaemia and the indication for PFO or ASD closure in these patients is questionable.

Conflicts of interest

None.

References