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Hemodynamics of patients developing pulmonary arterial hypertension after shunt closure

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ABSTRACT

Background: Pulmonary arterial hypertension (PAH) after shunt closure is associated with a poor prognosis. The aim of this study was to assess retrospectively the hemodynamics of patients developing PAH after shunt closure.
Methods: Hemodynamic data obtained by right heart catheterization (RHC) performed at baseline and after shunt closure were analyzed.
Results: Twenty-two patients, 13 with atrial septal defect (ASD), 6 with ventricular septal defect (VSD), 1 with patent ductus arteriosus, 1 with both ASD and VSD, and 1 with complete atrio-ventricular canal have been considered. The mean age at closure was 25.3 ± 20.1 years (range of 3 months to 56.7 years), and the mean age at PAH diagnosis was 37.0 ± 20.8 years (range of 5 to 61.2 years). The time delay between shunt closure and PAH diagnosis was 140.2 ± 100.2 months. At baseline RHC, hemodynamic data were as follows: pulmonary vascular resistance (PVR) of 8.6 ± 2.6 Wood units, PVR index (PVRi) of 10.1 ± 2.7 Wood units $*$ m^2, mean pulmonary arterial pressure of 43.7 ± 9.7 mm Hg, PVR to systemic vascular resistance ratio (PVR/SVR) of 0.70 ± 0.23, and Qp/Qs of 1.6 ± 0.4. In particular, 18/22 (81%) had PVR ≥ 5 Wood units, 21/22 (95%) PVRi ≥ 6 Wood units $*$ m^2, 21/22 (95%) PVR/SVR ≥ 0.33, and 11/22 (50%) Qp/Qs ≤ 1.5. During the follow-up, 5/22 (22%) patients died and one patient underwent successful double lung transplantation.
Conclusions: High baseline values of PVR (≥5 Wood units), PVRi (≥6 Wood units $*$ m^2) and PVR/SVR (≥0.33) are common findings in patients who develop PAH late after shunt closure. Large prospective clinical trials are needed to establish the safe limits for shunt closure.

1. Introduction

The clinical classification of congenital heart diseases (CHD) associated with pulmonary arterial hypertension (PAH) includes a condition that may occur after surgical or percutaneous closure of a cardiac shunt [1]. In these cases, CHD has been corrected but PAH is either still present immediately after shunt closure or has recurred several months or years after the procedure in the absence of significant postoperative residual congenital lesions or defects that originate as a sequela to previous surgery.

Patients who develop PAH after shunt closure have a poorer prognosis than patients with uncorrected PAH–CHD [2], which has raised concerns regarding correction of congenital heart defects in patients with overt PAH.

The recent grown-up congenital heart disease (GUCH) guidelines [3] suggest a Qp/Qs > 1.5 and a pulmonary vascular resistance (PVR) <5 Wood units as the hemodynamic upper limits for operability in patients with atrial septal defects (ASD) or ventricular septal defects (VSD), discouraging shunt closure in the presence of severe PAH or Eisenmenger syndrome.

The aim of this retrospective study was to assess hemodynamics in a consecutive cohort of patients referred to a single tertiary center for pulmonary hypertension (PH) who developed PAH after shunt closure.

2. Methods

2.1. Patient selection

All consecutive patients who referred to an Italian tertiary PH center (Monaldi Hospital, Second University of Naples, Italy) for PAH developed after surgical or percutaneous closure of a cardiac shunt were considered.

Concomitant causes of PH, such as lung or liver disease, were excluded using mandatory chest X-ray, respiratory function tests, perfusion lung scan, high-resolution computed tomography scan and abdominal ultrasound, according to current guidelines [1].

No lower or upper age limits were set.

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Informed consent (from the patient or the parents or the legal guardian, as appropriate) was obtained prior to entering the study. The protocol was approved by the institutional ethics committee. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

2.2. Study design

This was an open-label, retrospective study.

2.3. Clinical history

A complete clinical history was collected for each patient, including a detailed description of the underlying CHD, hemodynamic assessment by right heart catheterization (RHC) performed at baseline, type of correction, age at correction, prescribed therapy before and after shunt closure, presence of concomitant diseases, and the clinical course until referral for suspected PH.

2.4. Clinical evaluation

Clinical evaluation included assessment of WHO functional class and measurement of systemic arterial pressure, systemic pulse oximetry (SpO_2) and heart rate. Resting systemic arterial oxygen saturation was measured by non-invasive finger pulse oximetry after 5 min of absolute rest in sitting position, and the mean of three consecutive readings was recorded for analysis. Clinical findings such as pretibial edema, jugular venous pulse and hepatomegaly were observed.

Exercise capacity was evaluated with a non-encouraged 6-minute walk test [5,6]. The 6-minutewalk distance was calculated as the longest distance covered on two consecutive tests performed after 60–90 min. Heart rate and SpO_2 were recorded at rest and after exercise. The Borg dyspnea index was obtained immediately after completion of the test. The 6-minute walk test was performed in a 25-m-long corridor under the same environmental conditions and at approximately the same time of the day (±2 h).

2.5. Right heart catheterization

Hemodynamic assessment for suspected PH was performed by follow-up RHC according to current guidelines [1]. Right atrial, pulmonary artery, and pulmonary capillary wedge pressures as well as systemic pressure were recorded at the end of a quiet respiratory cycle. SpO_2 in the superior vena cava, inferior vena cava, pulmonary artery and femoral artery was measured in triplicate. Pulmonary venous saturation was measured in patients with ASD or assumed as 96% in the remaining cases, according to medical literature on CHD–PAH [7]. Pulmonary and systemic blood flows were obtained with the Fick principle using table-derived oxygen consumption values and calculated oxygen content at the corresponding sites [8] in order to exclude the presence of residual shunts.

2.6. Exclusion criteria

Patients who did not undergo preoperative hemodynamic assessment by RHC or with significant postoperative residual congenital lesions or defects developing as a sequela to previous surgery were excluded.

2.7. Statistical analysis

Variables are presented as mean ± SD. Changes from baseline to 6-month follow-up were evaluated using paired Student's *t* test for continuous and non-continuous variables. A p value of <0.05 was considered statistically significant. All reported p values are two-tailed. Statistical analyses were performed using a commercially available SPSS software package (v. 14.0 2008; SPSS Inc., Chicago, Illinois).

3. Results

Thirty consecutive patients (20 female) who developed PAH after shunt closure were evaluated. Eight out of 30 were excluded because of the lack of preoperative hemodynamic assessment (n = 6) and the presence of significant sequelae (n = 2). Of the remaining 22 patients (17 female), 13 had ASD, 6 had VSD, 1 had patent ductus arteriosus, 1 had both ASD and VSD, and 1 had complete atrio-ventricular canal (AVC). One out of 22 patients (4.5%) had Down's syndrome (the patient with AVC).

No patient showed right heart failure or signs/symptoms related to PAH at 12 months after shunt closure.

The mean age at closure was 25.3 ± 20.1 years (range of 3 months to 56.7 years), and the mean age at PAH diagnosis was 37.0 ± 20.8 years (range of 5 to 61.2 years). The time delay between shunt closure and PAH diagnosis at follow-up RHC was 140.2 ± 100.2 months (range of 40 to 358 months).

Baseline and follow-up hemodynamic data are reported in Tables 1 and 2, respectively. Notably, at baseline evaluation, 18/22 patients (81%) had PVR ≥5 Wood units and 21/22 patients (95%) had PVR index (PVRi) ≥6 Wood units $*$ m^2. In addition, 21/22 patients (95%) had a PVR to systemic vascular resistance (PVR/SVR) ratio ≥ 0.33, and 11/22 patients (50%) had a Qp/Qs ≤ 1.5. Fig. 1 displays changes in PVR from baseline to follow-up RHC.

Table 3 shows the clinical follow-up data of the study population and patient outcome.

The time from PAH diagnosis at follow-up RHC to the end of the observation period was 4.4 ± 2.1 years (range of 1.2 to 8.2 years). During follow-up, 5/22 patients (22%) died and one patient underwent successful double lung transplantation.

4. Discussion

Our study results show that baseline PVR ≥ 5 Wood units, PVRi ≥ 6 Wood units $*$ m^2 and PVR/SVR ≥ 0.33are common findings in patients who develop PAH late after shunt closure.

According to the recent GUCH guidelines [3], patients with ASD having significant left-to-right shunting (Qp/Qs > 1.5 or signs of right ventricular volume overload) and PVR <5 Wood units should undergo ASD closure regardless of symptoms. Similarly, patients with VSD are ideal candidates for closure if Qp/Qs is >1.5 and PVR is normal (<5 Wood units). More recently, on the basis of current knowledge, Beghetti et al. [9] suggested a PVR < 6 Wood units together with a PVR/SVR ratio ≥0.3 following 12 months of PAH-specific therapy as the hemodynamic upper limit for operability. Consistent with the literature, in the present study patients who developed PAH after defect closure were likely to have PVR ≥5 Wood units at baseline evaluation (81% in our retrospective series). This PVR threshold may reflect a reliable hemodynamic marker of pulmonary vascular disease due to increased shear stress and circumferential stretch with subsequent endothelial dysfunction and vascular remodeling. Nevertheless, pulmonary vascular involvement as well as PVR and PVR/SVR values form a continuous spectrum of variation, which makes difficult to establish unquestionable limits that mark a point of no return.

Notably, although a Qp/Qs > 1.5 is considered reassuring for shunt treatment, in our series 10/22 (45%) patients had Qp/Qs > 1.5 and 2/22 (9%) had Qp/Qs > 2 at baseline. It remains a clinical conundrum why patients with quite favorable hemodynamics (i.e., Qp/Qs > 1.5 and PVR < 5 Wood units as in our patients 3 and 8) develop PAH after shunt closure. It seems likely that a genetic predisposition or a subtle endothelial dysfunction may result in overt pulmonary vascular disease also in those patients who represent the best of the hemodynamic spectrum. A Qp/Qs > 2 may therefore be considered more appropriate to identify patients at low risk of developing PAH after shunt closure.

Since that mean pulmonary arterial pressure (mPAP) depends on pulmonary flow (Q), capillary wedge pressure (PCWP) and vascular resistance [mPAP = PCWP + (PVR $*$ Q)], it is not surprising that mPAP before shunt closure is a poor predictor of pulmonary vascular disease. Elevated mPAP values may result from high flow conditions, typical of younger age, or high Qp/Qs. On the contrary, from a pathophysiological point of view, the increase in PVR (or PVRi) and PVRi/SVRi ratio is more likely related to significant pulmonary vascular involvement.

In clinical practice, if PVR is above the recommended limits for surgical correction (>5 or 6 Wood units), a careful evaluation of pulmonary vascular reactivity should be performed to achieve the lowest PVR. In our retrospective series, only few patients (8/22) underwent acute vasoreactivity test. Because of the paucity of data and the different tests available (hyperoxia test using 100% FiO_2, inhaled nitric oxide at 10 to 20 ppm, epoprostenol), this issue was not taken into consideration.

Remarkably, no patient of our series showed right heart failure or signs/symptoms related to PAH at 12 months after shunt closure. In addition, the mean time delay between shunt closure and PAH diagnosis was longer than 10 years (140.2 ± 100.2 months). This suggests that