Pulmonary hypertension and congenital heart disease: An insight from the REHAP National Registry

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A B S T R A C T

Background: Pulmonary arterial hypertension (PAH) is common in patients with congenital heart disease (CHD). Although Eisenmenger syndrome may be on decline, other types of PAH–CHD are increasing and little is known on long-term outcome of this population. We report the PAH–CHD population of Spain via a national registry with focus on long-term survival.

Methods and results: A total of 240 consecutive patients (age 37.7 ± 14.1 years, 67.9% females) with PAH–CHD included in the REHAP registry were analysed. Patients were classified into 3 groups: 1) Eisenmenger syndrome, 2) postoperative-PAH and 3) PAH associated with small defects. Over a median follow-up time of 4.5 [1.6–7.1] years, 50 patients (20.8%) died or underwent lung/heart-lung transplantation. Patients with Eisenmenger syndrome had better survival than postoperative-PAH (HR 0.1 95% CI: 0.2–0.9, p = 0.048) but no advantage compared to small defects (HR 4.4, 95% CI 0.6–31.4, p = 0.15). In the overall PAH–CHD population, patients in NYHA functional class III–IV had a 3-fold increased risk of death (HR 3.0, 95% CI: 1.5–5.9, p = 0.001). Amongst patients with Eisenmenger syndrome, a pre-tricuspid shunt had a 2.6-fold increased risk of death (HR 2.6, 95% CI: 1.2–5.6, p = 0.03). There was no significant difference in survival between patients with postoperative-PAH and patients with IPAH (HR 0.99 95% CI: 0.6–1.7, p = 0.97).

Conclusion: PAH–CHD is associated with mid to long-term mortality. Outcome relates closely to functional class, type of PAH–CHD and within the Eisenmenger cohort, with location of the shunt. Adults with postoperative-PAH have the worse prognosis in the PAH–CHD cohort, reinforcing the need for lifelong close follow-up of such patients.

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1. Introduction

Pulmonary arterial hypertension (PAH) is commonly encountered in patients with congenital heart disease (CHD) and significantly affects outcome [1,2]. Eisenmenger syndrome, the extreme end of the spectrum of CHD related PAH (PAH–CHD), has attracted major attention over the past decade or two [3–11]. In fact, most of our knowledge on the pathophysiology and management of PAH–CHD is confined to patients with Eisenmenger syndrome.
With major advances in paediatric cardiology, allowing early detection and repair of congenital heart defects, the Eisenmenger population is decreasing in numbers, at least in the western world. Despite this, PAH–CHD remains prevalent and one of the most common types of PAH, as other non-Eisenmenger types of PAH–CHD are increasingly encountered [12].

While there are obvious differences in pathophysiology between PAH–CHD subgroups, little is known on their long-term outcome. Even within the Eisenmenger subgroup, it remains unclear whether the location of the defect determines cardiac adaptation and thus potentially outcome [13].

We report herewith the PAH–CHD population in Spain via a national registry [14], including all major centres managing such patients throughout the country. We focused on mid to long-term survival of patients with established, unequivocal pulmonary vascular disease, – thus excluding patients with a left to right shunt – and examined differences between subgroups.

2. Methods

2.1. Study population

The design of the REHAP registry has been previously described [14]. REHAP is a voluntary registry involving 31 hospitals in Spain designed to collect information on the demographics, management and outcome of newly and previously diagnosed patients with PAH (World Health Organization group 1) and patients with chronic thromboembolic pulmonary arterial hypertension.

The REHAP registry started in July 2007. Patients diagnosed with PAH after this time were prospectively included in the database. Moreover, patients who were followed in the participating centres and diagnosed after January 1998 were also retrospectively included in the registry and subsequently in the analysis. For the purpose of this report follow-up, data up to the end of May 2013 were extracted and fully analysed.

Confirmation of PAH on cardiac catheterization (mean pulmonary artery pressure (PAP) ≥25 mm Hg at rest with pulmonary artery wedge pressure ≤15 mm Hg) was required in all patients with the exception of those with Eisenmenger syndrome due to a post-tricuspid shunt. In the latter, PAH could be established by echocardiography alone, through the presence of low-velocity bidirectional or right-to-left shunt through the defect, in the absence of right ventricular outflow tract obstruction. Right heart catheterization was mandatory for diagnosing Eisenmenger syndrome in patients with a pre-tricuspid shunt. In the latter Eisenmenger syndrome was diagnosed when the Qp:Qs was ≤1 and indexed pulmonary vascular resistance > 8 Wood units/m².

Patients in this registry were classified into 3 groups, according to the latest ESC guidelines [12]: 1) Eisenmenger syndrome, 2) patients with PAH after cardiac defect repair (postoperative-PAH), developed at any point after defect closure and 3) patients with PAH associated with small cardiac defects (atrial septal defect (ASD) <2 cm or ventricular septal defect (VSD) <1 cm). Patients with pulmonary hypertension associated with left-to-right shunting in the presence of a large defect were not included in the registry, primarily because of uncertainty in defining and confirming PAH in this group of patients. Patients with an univentricular heart and any degree of pulmonary stenosis were also excluded, patients with a forced expired volume in 1 second (FEV1) ≤60% and/or forced vital capacity (FVC) ≤70%, in which pulmonary hypertension may be multifactorial, were also excluded from the analysis.

Patients were further classified according to cardiac anatomy into those with a simple or a complex defect. Simple defects included isolated ASD, partial anomalous venous drainage (PAPVD), VSD; and patent ductus arteriosus (PDA). All other defects were considered complex. Finally, patients were classified into those with pre-tricuspid versus post-tricuspid shunts, according to the location of the defect.

Data collected at baseline included age, sex, New York Heart Association (NYHA) functional class, type, location and size of the cardiac defect, shunt direction, associated extracardiac abnormalities, prior palliative or corrective surgery (including type of and age at repair), pulmonary function tests, six minute walk distance (6MWD), hemodynamic measurements, including acute vasodilator testing when available, and specific PAH treatment.

Data on all patients with idiopathic pulmonary arterial hypertension (iPAH) enrolled in the REHAP registry over the study period were also used in the analysis, for comparison with regard to survival between this patients and patients with post-operative-PAH.

2.2. Statistical analysis

Continuous variables are presented as mean ± standard deviation or median [interquartile range (IQR)], depending on data distribution, which was assessed for normality using the Shapiro–Wilk test. Categorical variables are presented as number (percentage). Comparison between groups was performed using Wilcoxon rank sum test or Chi-squared test, as appropriate.

Univariate Cox proportional-hazards regression analysis was used to compare all cause mortality between diagnostic groups. Kaplan–Meier curves were also plotted and the Log-rank test between groups was reported. For the purpose of the survival analysis, the date of the first confirmatory right heart catheterization was used as date of diagnosis in all patients, except patients with Eisenmenger syndrome due to a post-tricuspid shunt. In the latter, in which diagnosis of Eisenmenger syndrome was established by echocardiography, the date of inclusion in the registry was used as time 0 (baseline) for the purpose of the survival analysis. Patients were censored at their latest follow-up or at time of transplantation.

A two-sided p-value of <0.05 was considered indicative of statistical significance. Statistical analysis was performed using SPSS version 19 (SPSS Inc., Chicago, Illinois) and R version 2.15.0 (http://cran.r-project.org/) statistical software.

3. Results

3.1. Population characteristics

3.1.1. Overall population

From 1st July 2007 to 31st May 2013, 240 patients with PAH–CHD were enrolled in REHAP. Almost half of these patients (45.8%) were newly diagnosed after 2007, whereas 130 (54.2%) were included retrospectively, as they had been diagnosed between 1998 and 2007. Mean age at the time of diagnosis was 37.7 ± 14.1 years and 160 (66.7%) were female. The majority of patients had Eisenmenger syndrome (163 patients, 67.9%). Fifty-seven patients (23.8%) had postoperative-PAH, while only 20 patients (8.3%) had pulmonary hypertension in the presence of a small defect. From an anatomical point of view, the majority of patients had simple defects (152 patients, 63.3%) while only 88 (36.7%) had complex defects (Table 1). VSD was the most common diagnosis (73 patients, 30.4%), followed by ASD (56 patients, 23.3%) and atrio-ventricular septal defect (AVSD, 68 patients, 20.8%).

The majority of patients were in NYHA functional class II or III (205 patients, 85.4%) and only 18 patients (7.5%) were in NYHA functional class IV. The overall median 6MWD was 370.0 [280.0–451.0] metres (m) and was significantly lower in patients with Eisenmenger syndrome compared to patients with postoperative-PAH (357.0 [280.0–430.0] m vs 404.0 [324.8–492.0] m, p = 0.004).

The most common symptom was dyspnoea, present in 90.4% of patients. A quarter of the patients (25.8%) had signs of heart failure. The majority of patients received PAH-specific therapies at some point during their follow-up (179 patients, 74.6%). The median time from diagnosis to treatment was 1.7 [IQR: 0.1–9.9] months. The most common first line treatment was an endothelium receptor antagonist (ERA) (108
patients, 60.3%), followed by phosphodiesterase type 5 (PDE-5) inhibitors (34 patients, 19.0%). Prostacyclins were used as first line therapy in 20 patients (11.3%), while 17 patients (9.5%) were started on upfront combination therapy (Table 1).

3.1.2. Eisenmenger patients

The majority of patients with Eisenmenger syndrome were female; their age at baseline was 36.3 ± 78.4 years. A post-tricuspid shunt was present in the vast majority of patients with Eisenmenger syndrome (145 patients, 89.0%). The most common lesion amongst this population was an isolated VSD (57 patients, 35.0%), followed by an AVSD (33 patients, 20.2%). Patients with post-tricuspid shunts were younger at baseline (35.5 ± 12.3 vs 42.8 ± 13.6 years, p = 0.02) and had better exercise capacity (360 [272.0–450.0] m vs 290 [166.0–375.0] m, p = 0.04) compared to patients with pre-tricuspid shunts. Approximately half of the patients with a post-tricuspid shunt were in NYHA functional class III–IV, compared to over two thirds of cases (64.0% vs 37.5%, p = 0.002) compared to patients without Down syndrome. These patients were more likely to have developed syncope in the past (6.9% vs 33.3%, p = 0.001).

Fifty patients (30.7%) with Eisenmenger syndrome had Down syndrome. These patients were more likely to have a complex defect (64.0% vs 37.5%, p = 0.002) compared to patients without Down syndrome. The most commonly encountered anatomic lesion in this population was an AVSD (28 patients, 56.0% of Down patients). Over two thirds of Eisenmenger patients (71.8%) received treatment with pulmonary vasodilators during follow-up. Oral therapy was used as first line in the vast majority of treated patients (81.2%). The most commonly used treatment was an ERA (78 patients, 66.7%), followed by a PDE-5 inhibitor (17 patients, 14.5%). Prostanoids were given as first line in the vast majority of treated patients (81.2%). The most commonly used treatment was an ERA (78 patients, 66.7%), followed by a PDE-5 inhibitor (17 patients, 14.5%). Prostanoids were given as first line therapy to 20% of treated patients.

Table 1

Baseline characteristics.

<table>
<thead>
<tr>
<th>Type of defect</th>
<th>All No (%)</th>
<th>Eisenmenger Postoperative Small shunt p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular septal defect</td>
<td>73 (30.4)</td>
<td>57 (35.0)</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>56 (23.3)</td>
<td>18 (11.0)</td>
</tr>
<tr>
<td>Atrioventricular septal defect</td>
<td>38 (15.8)</td>
<td>33 (20.2)</td>
</tr>
<tr>
<td>Ductus arteriosus</td>
<td>19 (7.9)</td>
<td>14 (8.6)</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>14 (5.8)</td>
<td>14 (8.6)</td>
</tr>
<tr>
<td>Univentricular heart</td>
<td>10 (4.2)</td>
<td>6 (3.1)</td>
</tr>
<tr>
<td>Isolated PAVD</td>
<td>4 (1.7)</td>
<td>–</td>
</tr>
<tr>
<td>TGA + VSD</td>
<td>5 (2.1)</td>
<td>5 (3.1)</td>
</tr>
<tr>
<td>Combined (&gt;2) defects</td>
<td>21 (8.8)</td>
<td>12 (7.4)</td>
</tr>
<tr>
<td>NYHA III–IV (n, %)</td>
<td>135 (56.3)</td>
<td>99 (60.7)</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>370.0 [280.0–451.5]</td>
<td>357.0 [260.0–432.0]</td>
</tr>
</tbody>
</table>

Table 2

Baseline characteristics of Eisenmenger patients according with the location of the shunt.

<table>
<thead>
<tr>
<th>No (n, %)</th>
<th>Pre-tricuspid Post-tricuspid p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years)</td>
<td>18 (11.0)</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>42.8 ± 13.6</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>15 (83.3)</td>
</tr>
<tr>
<td>NYHA III–IV (n, %)</td>
<td>15 (83.3)</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>290 [166.0–375.0]</td>
</tr>
</tbody>
</table>

All data are expressed as mean ± SD or n (%). Six minute walk distance is expressed as median [IQR]. ERA: endothelin receptor antagonist; NYHA: New York Heart Association; PAVD: pulmonary anomalous venous drainage; mPAP: mean pulmonary artery pressure; mRAP: mean right atrial pressure; PDE: phosphodiesterase; PVR: pulmonary vascular resistance; TGA: transposition of the great arteries; VSD: ventricular septal defect; 6MWD: six minute walk distance.
first line therapy in 12 patients (10.3%). Intravenous prostacyclin was only used in 3 patients (2.6%), all of them with a pre-tricuspid shunt. Ten patients (8.5%) received combination therapy as a first line, which was more common amongst patients with a pre-tricuspid shunt (21.1% vs 4.2%, p = 0.02).

3.1.3. Postoperative-PAH–CHD

Postoperative-PAH was present in 57 (23.8%) of patients in our cohort. Mean age at baseline was 39.8 ± 17.0 years and two thirds were female (66.7%). Almost half (47.4%) of the patients were in NYHA functional class III or IV and a quarter of patients (28.1%) had signs of heart failure at the time of diagnosis. Most patients had a simple defect (75.4%); an ASD was the most commonly repaired defect (22 patients, 38%), followed by a VSD (12 patients, 21.1%) and a PDA (5 patients, 8.8%). Only 5 patients (8.8%) had repair of a complex defect and in 9 patients (15.8%) more than one defect had been repaired. Mean age at repair was 21.9 ± 23.6 years. Patients with an ASD were older at the time of repair (42.3 ± 23.2) than patients with a VSD (9.1 ± 12.5, p < 0.001), a PDA (11.9 ± 9.9, p = 0.009) or AVSD (48 ± 6.3, p < 0.001). Mean pulmonary artery pressure was significantly lower in patients with postoperative-PAH compared to Eisenmenger patients (54.2 ± 17.3 vs 70.1 ± 16.0, p < 0.001) however right atrial pressure was significantly higher (11.7 ± 6.5 vs 8.5 ± 4.9, p = 0.003). Unfortunately haemodynamic data at the time of repair were not available.

The majority of patients (80.7%) received treatment with pulmonary vasodilators during follow-up. Oral therapy was used as first line in almost three quarters of treated patients (73.9%). The most commonly used treatment was with an ERA (21 patients, 41.7%), followed by PDE-5 inhibitors (13 patients, 28.6%) and prostanoids (7 patients, 15.2%). Upfront combination therapy was used in 5 patients (10.9%).

3.1.4. Pulmonary hypertension associated with small defects

Pulmonary hypertension associated with small defects was present in 20 patients (8.3%), mean age was 42.5 ± 14.7 years and the majority were female (80%). The most common defect was an ASD (16 patients, 80%) and only 4 patients (20%) had a VSD.

There was no significant difference in mean pulmonary artery pressure between patients with small defects and patients with postoperative-PAH (50.5 ± 13.6 vs 54.2 ± 17.3, p = 0.066), but right atrial pressure was significantly lower in the former (7.7 ± 4.6 vs 11.7 ± 6.5, p = 0.02). Furthermore, there was no difference in right atrial pressure between patients with small defects and Eisenmenger patients (7.7 ± 4.6 vs 8.5 ± 4.9, p = 0.51), even though mean pulmonary artery pressure was significantly higher in the latter (70.1 ± 16.0 vs 50.5 ± 13.6, p < 0.001).

Pulmonary vasodilators were prescribed in the majority of patients (16 patients, 80%) during follow-up. ERAs were most commonly used (9 patients (56.3%)) while prostanoids were used in only 1 patient (6.3%).

3.1.5. PAH–CHD and outcome

Over a median follow-up time of 4.5 [1.6–7.1] years, 36 (15.0%) patients died and 14 (5.8%) underwent transplantation, heart-lung transplantation was performed in 12 (85.7%), while the remaining 2 (14.3%) underwent bilateral lung transplantation. Nineteen patients (7.9%) were lost to follow-up at a median time of 0.9 [0.3–2.6] years from baseline and were censored at the last follow-up visit for the purpose of survival analysis. Overall survival (freedom from death or transplantation) in this population was 90.5%, 77.6%, 68.9% and 52% at 1, 3, 5, and 10 years. Survival in this group resembled closely to patients with postoperative-PAH (HR 0.99 95% CI: 0.6–1.7, p = 0.97) (Fig. 5) and was significantly worse compared to patients

No significant difference in survival was detected between small shunts and Eisenmenger patients (HR 4.4, 95% CI 0.6–31.4, p = 0.15) while patients with small shunts tended to have a better survival compared to postoperative-PAH patients (HR 7.6, 95% CI: 1.00–57.0, p = 0.049) (Fig. 3).

The impact of the location of the defect was assessed in the Eisenmenger population. In this subgroup, 25 patients (15.3%) died and 8 (4.9%) underwent heart and lung transplantation. Survival (freedom from death or transplantation) was 89.9%, 83.3%, 80.3% and 70.5% at 1, 3, 5 and 10 years respectively. The presence of a pre-tricuspid shunt (HR 2.6, 95% CI: 1.2–5.6, p = 0.03), and NYHA functional class III–IV (HR 3.2, 95% CI: 1.3–7.8, p = 0.006) were the strongest predictors of outcome in this population (Fig. 4).

3.1.6. Differences in outcome between iPAH and PAH–CHD

From 1st January 1998 to 31st May 2013, 409 patients with iPAH were included in REHAP; mean age was 47.7 ± 18.3 years; the majority of patients were female (212 patients, 71.4%). The overall survival (freedom from death or transplantation) in this population was 90.5%, 77.6%, 68.9% and 52% at 1, 3, 5, and 10 years. Survival in this group resembled closely to patients with postoperative-PAH (HR 0.99 95% CI: 0.6–1.7, p = 0.97) (Fig. 5) and was significantly worse compared to patients
with small shunts (HR 7.3 95% CI: 1.1–52.2, p = 0.048) or patients with Eisenmenger syndrome (HR 1.6 95% CI: 1.1–2.3, p = 0.08).

4. Discussion

This large national registry demonstrates that PAH–CHD is associated with mid to long-term mortality, rates of death or need for transplantation differ amongst different subgroups. Outcome relates closely to functional class, type of PAH–CHD and within the Eisenmenger cohort, with location of the shunt. While PAH–CHD patients overall have a better prognosis than those with iPAH, this is not the case with patients in which PAH develops or persists after repair of a congenital cardiac defect. It is, thus, very important to correctly classify PAH–CHD patients into diagnostic subgroups, as their pathophysiology and prognosis differ significantly and so should their management.

4.1. Pulmonary arterial hypertension after corrective surgery

Postoperative pulmonary arterial hypertension was present in a quarter of our population and had the worse prognosis. Pulmonary hypertension after correction of a cardiac defect can persist or develop many years after correction [15]. In many cases, postoperative-PAH is diagnosed after late correction of the defect [16], when irreversible pulmonary vascular disease is already established. This can be the case in our cohort since a high percentage of the patients had late repair.

Unfortunately hemodynamic data at the time or repair were not available in the registry. Surgical or transcatheter repair at late stage can adversely transform the prognosis as the defect, which was acting as a relief valve, is closed. While correct identification of patients who will benefit from defect closure is paramount, evidence-based criteria for defining operability are still lacking. The decision to repair any defect in patients with PAH should be taken by tertiary centres with expertise in PAH–CHD, based not only on hemodynamic data, but considering previous history and all clinical information.

To our knowledge, this is the first study to confirm that patients with postoperative-PAH have similar prognosis to patients with iPAH, which is significantly worse to that of adult Eisenmenger patients, despite higher pulmonary resistances in the latter. In fact, while pulmonary vascular resistance is a good marker of the severity of pulmonary vascular disease, right ventricular adaptation is the most important determinant of survival in PAH [17,18]. In iPAH and postoperative-PAH, the RV adapts less well to the increase in afterload, compared to Eisenmenger syndrome. Myocardial hypertrophy develops but is inadequate for normalizing wall stress, thus, leading to progressive contractile dysfunction and chamber dilation [19]. The decline in contractility, increased sphericity of the right ventricle and subsequent reduction in right ventricular function lead to a drop in cardiac output, which cannot be compensated for by right-left shunting, as occurs in Eisenmenger patients. The presence of a high right atrial pressure in patients with postoperative-PAH compared to Eisenmenger patients or patients with small defects in our study, reflects worse right ventricular function, lower cardiac output and the inability of the right ventricle to relieve part of its load through shunting. This, in turn, is likely to result in a far worse long-term prognosis.

All patients who have undergone previous repair of CHD should be assessed for the presence of PAH, not only immediately after the operation, but throughout their life-long follow-up, as early identification is likely to significantly improve outcome [20]. Maintaining and regularly reviewing clinical records, including information on previous interventions, especially those performed in infancy, can aid clinicians experienced in CHD to identify patients at risk of developing any degree of residual postoperative PAH [21,22].

4.2. Eisenmenger syndrome

Eisenmenger syndrome, which was present in the majority of our patients, had the best prognosis, as has been previously reported [16]. Survival in this population relates to the location of the shunt, with patients who have a pre-tricuspid shunt demonstrating a 2.6-fold higher mortality compared to those with post-tricuspid shunts. This
substantial difference in outcome is likely to be related to different levels of right ventricular adaptation. In patients with a post-tricuspid shunt, pulmonary hypertension develops early in life or persists after birth, possibly allowing the right ventricle to train and adapt, maintaining a hypertrophied foetal phenotype. This, together with the presence of a defect, which allows the right ventricle to offload quite effectively, leads to better right ventricular systolic function, compared to patients with a pre-tricuspid shunt, in which the right ventricle behaves more like in iPAH, dilating and failing earlier. Differences in right ventricular function are likely to translate in different long-term survival. Moceri et al., in fact, recently reported that tricuspid annular systolic excursion and TDI (Tissue Doppler Imaging) peak systolic velocity of the lateral wall of the right ventricle, both makers of right ventricular function, were strong predictors of outcome in a large population of Eisenmenger patients [10].

The vast majority of Eisenmenger patients included in REHAP did report symptoms of exercise intolerance and a worse functional class was related to worse prognosis. Treatment with pulmonary vasodilators, which is certainly recommended in patients in NYHA functional class III or above[7,12], is likely to improve survival in this population [6]. Expertise is required in assessing functional class in Eisenmenger syndrome patients, in whom the condition has been present since childhood and who tend to adapt their activity to their abilities, thus, often overestimating their exercise tolerance. It is likely that, similar to other types of PAH, early initiation of pulmonary vasodilator will be beneficial also for patients with Eisenmenger syndrome in functional class II, as there is mounting evidence that this is a progressive condition with devastating long-term effects.

4.3. PAH–CHD in patients with small defects

Patients with PAH in the presence of a small cardiac defect was the smallest cohort in our population. Debate continues on whether these patients should be classified as PAH–CHD or iPAH with a coexistent defect. In fact, small cardiac defects are not expected to lead to the development of PAH and an intrinsic predisposition of the pulmonary vasculature is likely to contribute to the development of pulmonary vascular disease. However, the presence of a small defect may be beneficial long-term, especially in patients with significantly raised pulmonary vascular resistance and a failing right ventricle, by allowing right-to-left shunting which can partially “decompress” the RV and contribute to systemic cardiac output [23–26]. This is the theoretical basis for recommending atrial septostomy in patients with severe iPAH [12]. The vast majority of patients with small defects in our registry (80%) had a pre-tricuspid shunt, which may explain the better survival compared to post-operative patients in which the defect is closed and is congruous with previous studies [16,27,28].

4.4. Comparison to other registries of PAH–CHD

In our overall PAH–CHD population, 10 year survival was 67.1%, which appears optimal for patients with this condition and better than other types of PAH, but is lower than previously reported PAH–CHD cohorts. Manes et al. recently published a cohort of 192 patients with PAH–CHD showing an overall survival at 10 years of 85% [16]. Such differences in survival may be attributed to the relative case-mix of patients included in such registries. A higher survival is expected in patients with left to right shunt compared to other types of PAH–CHD. In fact, the majority of patients with left to right shunt, and especially those amenable to repair of the defect, have little pulmonary vascular disease and, thus, a much better prognosis. As the debate on hemodynamic cut-offs and other criteria for deciding reversibility and repairability continues, we opted to exclude this subgroup from the REHAP, in order to ensure that all patients in this registry had established pulmonary vascular disease. This is the most likely explanation of the difference in overall survival compared to previously reported cohorts [16] which included large numbers of patients with a left to right shunt.

4.5. Study limitations

The REHAP is an observational and voluntary registry including all national pulmonary hypertension centres and several smaller centres. As treatment of PAH in Spain is not restricted to specialist centres, it may be that not all PAH–CHD patients in Spain were included in the registry, but the vast majority of patients is likely to have been captured. To avoid “immortal time bias”, only patients managed in participating centres after 1st January 1998 were considered, ensuring that all patients managed from 1998 to 2013 were included, whether alive or deceased. For the same reason, baseline (time 0 for the survival analysis) for Eisenmenger syndrome patients (in the majority of whom the condition is present since childhood), was considered the date of enrolment in the registry.

5. Conclusions

The present study shows striking differences in survival between different groups of CHD–PAH. Adult patients with postoperative-PAH have the worse prognosis in the PAH–CHD cohort, very similar to that of iPAH patients, and therefore require special attention to ensure early diagnosis and treatment. Although the majority of patients were treated with advanced therapies during their follow-up, long-term comparative studies are required to determine the optimal timing of treatment in this population.

Conflict of interest

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References


