Epidemiology of pulmonary hypertension: new data from the Swiss registry

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Background: since 1999 data from pulmonary hypertension (PH) patients from all PH centres in Switzerland were prospectively collected. We analyse the epidemiological aspects of these data.

Methods: PH was defined as a mean pulmonary artery pressure of >25 mm Hg at rest or >30 mm Hg during exercise. Patients with pulmonary arterial hypertension (PAH), PH associated with lung diseases, PH due to chronic thrombotic and/or embolic disease (CTEPH), or PH due to miscellaneous disorders were registered. Data from adult patients included between January 1999 and December 2004 were analysed.

Results: 250 patients were registered (age 58 ± 16 years, 104 (41%) males). 152 patients (61%) had PAH, 73 (29%) had CTEPH and 18 (7%) had PH associated with lung disease. Patients <50 years (32%) were more likely to have PAH than patients >50 years (76% vs. 53%, p <0.005). Twenty-four patients (10%) were lost to follow-up, 58 patients (26%) died and 150 (66%) survived without transplantation or thrombendarterectomy. Survivors differed from patients who died in the baseline six-minute walking distance (400 m [300–459] vs. 273m [174–415]), the functional impairment (NYHA class III/IV 86% vs. 98%), mixed venous saturation (63% [57–68] vs. 56% [50–61]) and right atrial pressure (7 mm Hg [4–11] vs. 11 mm Hg [4–18]).

Discussion: PH is a disease affecting adults of all ages. The management of these patients in specialised centres guarantees a high quality of care. Analysis of the registry data could be an instrument for quality control and might help identify weak points in assessment and treatment of these patients.

Key words: pulmonary hypertension; epidemiology; registry

Summary

Pulmonary hypertension (PH) is a devastating disease leading to right heart failure and death. In the last 15 years, a better understanding of pathogenesis and risk factors has led to new diagnostic and therapeutic approaches and hence to an increased interest in detection of this incurable disease [1–3]. Since PH is a rare disease, information about epidemiology, follow-up and prognosis are difficult to obtain, but are invaluable to improve therapy and assess outcome parameters [4]. The Swiss Registry for Pulmonary Hypertension was initiated in 1999 with the aim to gain more insight into prevalence, epidemiology, therapy and outcome of patients with pulmonary hypertension in Switzerland. First retrospective data have been published in 2001 [5]. Since then, data...
from PH patients from all PH centres and associated hospitals in Switzerland were prospectively collected. In this study, we analyse the epidemiological aspects of these data and focus on basic clinical characteristics of PH patients and estimated burden of the disease in the population.

**Methods**

Prospective data collection took place in 5 University Hospitals (Basel, Bern, Geneva, Lausanne, Zurich) and in 4 associated hospitals (Aarau, Barmelweid, Locarno, St Gallen) in Switzerland. Patients with pulmonary arterial hypertension (idiopathic, associated with collagen vascular disease, portal hypertension, HIV infection, drugs or toxins), PH associated with lung diseases and/or hypoxaemia, PH due to chronic thrombotic and/or embolic disease, or PH due to miscellaneous disorders (sarcoidosis, histiocytosis X, lymphangiomatosus, compression of pulmonary vessels) were included in the registry. Patients with PH due to left heart disease were not included as well as three patients with pulmonary angiosarcoma. Due to a change in nomenclature in 2004, the term "idiopathic pulmonary arterial hypertension" (IPAH) includes both sporadic and familial cases of pulmonary arterial hypertension (PAH).

Pulmonary hypertension was defined as a mean pulmonary artery pressure of >25 mm Hg at rest or >30 mm Hg on exercise.

The following data were collected: age and gender of the patient, diagnosis according to the Evian clinical classification [6], date of diagnosis, height, weight, vital signs (blood pressure, heart rate and oxygen saturation at rest), NYHA class, six minute walking distance (6MWD), haemodynamics assessed by right heart catheterisation (systolic pulmonary artery pressure, mean pulmonary artery pressure (PAPmean), right atrial pressure, cardiac output, mixed venous oxygen saturation, pulmonary vascular resistance, response to vasoreactivity testing, tricuspid pressure gradient measured with transthoracic Doppler echocardiography, liver enzymes, creatinine, coagulation studies (INR and current medication (diuretics, anticoagulation, calcium antagonists, iloprost, bosentan, sildenafil, oxygen). A positive response to vasoreactivity testing was defined as a decrease of PAPmean of more than 10 mm Hg, to a value lower than 40 mm Hg, with a normal or high cardiac output [7]. The tricuspid pressure gradient was calculated from the maximal transtricuspid jet in Doppler echocardiography using the modified Bernoulli equation.

Whether a patient was included in the registry or not was at discretion of the treating PH specialist. When a patient was included in the registry, data collection started at the first visit of the patient in the PH centre or associated hospital, and continued every 3 to 6 months until occurrence of one of the clinical endpoints (death, lung transplantation, pulmonary thromboendarterectomy). The clinical follow-up of the patients was performed as usual irrespective of whether a patient was included in the registry or not.

In this study, we analyse data from adult patients (>18 years of age) that were included in the registry between January 1999 and December 2004 (table 1).

**Statistics**: in descriptive analyses we report median [interquartile range] for continuous parameters and for categorical parameters frequency distribution.

For estimation of prevalence and incidence of PH in Switzerland we assumed an adult population of 6 million inhabitants [8]. The prevalence of PH for the year 2004 was calculated by dividing the number of patients diagnosed with PH and included in the registry before 2004, and known to be alive in 2004, by the approximate number of adult Swiss inhabitants. Incidence estimates were calculated for each year by dividing the number of patients diagnosed with PH and included in the registry each year by the approximate number of adult Swiss inhabitants (6 million).

For survival analyses, follow-up time was calculated from date of registration in the registry until last clinical visit or the date of death. Differences between the two outcome groups (survivors and non-survivors) were described by presenting Kaplan–Meier survival curves for selected variables. Analysis was performed with STATA 9.1 software (Stata Corp LP, Texas, USA).

**Ethics**: written informed consent was obtained from each patient before inclusion in the registry.

### Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients included</td>
<td>15</td>
<td>16</td>
<td>18</td>
<td>47</td>
<td>63</td>
<td>59</td>
<td>250</td>
</tr>
<tr>
<td>Lost of follow-up</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>10</td>
<td>24</td>
</tr>
</tbody>
</table>

Number of patients included in the registry each year

### Results

A total of 252 adult patients were included in the registry between January 1999 and December 2004. Two patients with PH due to left heart disease were mistakenly included in the registry, and were excluded from further analysis. Median follow-up of the remaining 250 patients was 18.8 [9–31] months. Median time between successive visits was 3 [2–5] months. There were more female (147; 59%) than male patients. Median age was 59 [46–70] years for female patients, and 63 [45–70] years for male patients. Most patients (90%) had either PAH or chronic thrombotic/embolic pulmonary hypertension (CTEPH). Further information about baseline characteristics of patients and aetiology is given in table 2. About one third (32%) of patients were younger than 50 years. Of these, 76% had PAH, whereas only 53% of patients over 50 years of age had PAH. Age distribution is shown in figure 1.
Seventy-one of the 250 patients had no right-heart catheter data in the registry (28%). Of the remaining 179 patients, 119 (66%) had vasoreactivity testing. A first analysis gave 38% of responders, which appeared much higher than reported in the literature. So right heart catheter data were verified in the source document in 118 of 250 patients. Of these 118 patients, 31 patients did not have a right-heart catheter, and 16 had a catheter but no vasoreactivity testing. In the remaining 71 patients, vasoreactivity was verified according to the criteria described above. New analysis gave an overall responder rate of 20% (table 2). Patients with IPAH were significantly more likely to respond to vasoreactivity testing than were patients with other aetiologies for PH (p = 0.03).

In 2004 we estimated the prevalence of PH of any aetiology in Switzerland at about 25 patients per one million adult inhabitants. For PAH prevalence was 15.5 patients, and for IPAH 8.6 patients per one million adult inhabitants respectively. The incidence of PAH was estimated to have increased from 1.2 patients per one million adult inhabitants in 1999 to 3.5 patients per one million adult inhabitants in 2004. Respective data for IPAH were 0.8 patients per one million adult inhabitants in 1999 and 1.2 patients per one million adult inhabitants in 2004.

Twenty-four patients (10%) were lost to follow-up. Of the remaining 226 patients, 58 (26%) died, 7 (3%) had pulmonary thrombendarterectomy (TEA) for CTEPH, 10 (4%) underwent lung transplantation, 1 patient had liver transplantation, and 150 patients (66%) survived without TEA or transplantation. Median time between diagnosis and death was 23.5 months, range 4–196 months. Characteristics of patients who survived without TEA or transplantation (“survivors”) and patients who died are shown in Table 3. Survival as a function of different baseline parameters is shown in figure 2.

### Table 2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total N = 250</th>
<th>IPAH N = 70</th>
<th>CTEPH N = 73</th>
<th>CVD N = 41</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>41</td>
<td>36</td>
<td>45</td>
<td>24</td>
</tr>
<tr>
<td>Female</td>
<td>59</td>
<td>64</td>
<td>55</td>
<td>76</td>
</tr>
<tr>
<td><strong>Age (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 y</td>
<td>12</td>
<td>34</td>
<td>16</td>
<td>29</td>
</tr>
<tr>
<td>&gt;50 y</td>
<td>68</td>
<td>66</td>
<td>84</td>
<td>71</td>
</tr>
<tr>
<td><strong>NYHA (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>II</td>
<td>12</td>
<td>10</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>III</td>
<td>62</td>
<td>70</td>
<td>57</td>
<td>34</td>
</tr>
<tr>
<td>IV</td>
<td>25</td>
<td>20</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>242</td>
<td>69</td>
<td>73</td>
<td>39</td>
</tr>
<tr>
<td><strong>6MWD (m)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean pulmonary artery pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>176</td>
<td>51 [40–64]</td>
<td>46 [35–56]</td>
<td>43 [34–51]</td>
</tr>
<tr>
<td><strong>Pulmonary vascular resistance (dyne.s.cm⁻²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mixed venous oxygen saturation (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac output (l/min)</strong></td>
<td>3.9 [3.2–5.0]</td>
<td>4.0 [3.3–5.2]</td>
<td>3.6 [3.0–4.2]</td>
<td>4.1 [3.0–5.3]</td>
</tr>
<tr>
<td>n</td>
<td>151</td>
<td>47</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td><strong>Tricuspid regurgitation pressure gradient (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Responder in vasoreactivity testing (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>71</td>
<td>35</td>
<td>8</td>
<td>20</td>
</tr>
</tbody>
</table>

Baseline characteristics of patients included in the Swiss Pulmonary Hypertension Registry. For continuous data median and [interquartile range] are shown. Not shown are following aetiologies (number of patients): PAH associated with congenital shunts (10), with portal hypertension (1), with HIV (10), with drugs (3), PAH not further specified (17), pulmonary veno-occlusive disease (1), PH associated with hypoxemia or lung disease (18). PH associated with miscellaneous diseases (6).
Table 3

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Survived N = 150</th>
<th>Died N = 58</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPAH</td>
<td>30%</td>
<td>26%</td>
</tr>
<tr>
<td>CTEPH</td>
<td>31%</td>
<td>24%</td>
</tr>
<tr>
<td>CVD</td>
<td>14%</td>
<td>21%</td>
</tr>
<tr>
<td>Other</td>
<td>25%</td>
<td>29%</td>
</tr>
<tr>
<td>NYHA class III or IV</td>
<td>86%</td>
<td>98%</td>
</tr>
<tr>
<td>Male gender</td>
<td>38%</td>
<td>41%</td>
</tr>
<tr>
<td>Responder in vasoreactivity testing</td>
<td>21%</td>
<td>20%</td>
</tr>
<tr>
<td>6-minute walking distance (m)</td>
<td>400 [300–459] (134)</td>
<td>273 [174–415] (49)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>124 [110–139] (148)</td>
<td>120 [110–140] (54)</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mm Hg)</td>
<td>47 [36–57] (107)</td>
<td>51 [39–53] (17)</td>
</tr>
<tr>
<td>Systolic pulmonary artery pressure (mm Hg)</td>
<td>74 [59–90] (101)</td>
<td>79 [63–101] (34)</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyn.s.cm⁻¹)</td>
<td>690 [460–1080] (96)</td>
<td>890 [570–1220] (31)</td>
</tr>
<tr>
<td>Cardiac Output (l/min)</td>
<td>4.0 [3.4–5.1] (92)</td>
<td>3.3 [3.3–5.3] (29)</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation (%)</td>
<td>61 [57–68] (88)</td>
<td>56 [50–61] (31)</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>7 [4–11] (81)</td>
<td>11 [4–18] (31)</td>
</tr>
<tr>
<td>Tricuspid pressure gradient (mm Hg)</td>
<td>62 [54–80] (116)</td>
<td>69 [57–82] (42)</td>
</tr>
<tr>
<td>Age at diagnosis (y)</td>
<td>59 [44–60] (150)</td>
<td>60 [44–70] (58)</td>
</tr>
</tbody>
</table>

Baseline characteristics of patients who survived without transplantation or thrombendarterectomy and patients who died during follow-up. For continuous data, median and [interquartile range] (sample size) are shown.

Discussion

Analysis of the Swiss Registry for Pulmonary Hypertension yields an estimation of prevalence and incidence of this disease in Switzerland and gives some insights in the clinical characteristics of patients with PH. However, the registry has some limitations. Although comprehensive information has been provided to potential referring physicians all over Switzerland we cannot assume that every patient diagnosed with PH in Switzerland is included in the registry. Further, it is likely that patients with functional class I and II are under-represented probably in part because they are under-diagnosed. Moreover, the assessment of patients with PH in the different participating centres is not identical, and the completeness of data entered into the register varies.

The conservative estimates of the prevalence of PAH and IPAH in Switzerland in 2004 based on our registry are within the range of the data from the French Network on Pulmonary Arterial Hypertension with an estimated prevalence of 15 and 5.9 cases respectively per one million adult inhabitants [11]. Both the French and Swiss registries show a lower prevalence of this disease than the recently published data from the Scottish population [26]. Peacock and co-workers found a
parameters like mean pulmonary artery pressure, others [5, 12]. In contrast to other publications, parameters. Pulmonary vascular resistance is nei-
tance of central venous saturation [10], NYHA
monary Hypertension [5] confirming the impor-
t from 1991–1999 from the Swiss Registry for Pul-
erstudies, including the retrospective data
There are no gender differences in mortality. Our patients are still detected at an advanced
stage of the disease, with a mean pulmonary ar-
ty pressure of 50 mm Hg and 87% of patients
ating NYHA class III or IV dyspnoea at diagno-
sis. Reasons for this late detection might still be an insufficient awareness of the disease and the
underuse of echoangiography and diffusion ca-
pacity measurements in the workup of patients
with unexplained dyspnoea. It is also the hallmark
of the disease itself, which progresses insidiously
without specific clinical signs or symptoms until
late, when right heart failure and severe distur-
bance of gas exchange is present.
Overall mortality over 5 years’ follow-up of
patients with PH of any aetiology included into the
Swiss registry between 1999 and 2004 was 26%. There is no gender difference in mortality. In this study 6MWD, NYHA class, right atrial pressure and mixed venous saturation seem to be important prognostic parameters. There are other studies, including the retrospective data from 1991–1999 from the Swiss Registry for Pulmonary Hypertension [5] confirming the import-
tance of central venous saturation [10], NYHA functional class [9, 13], right atrial pressure [9, 15] and 6-minute walking distance [12] as prognostic parameters. Pulmonary vascular resistance is nei-
ther a predictor of mortality in this study nor in
others [5, 12]. In contrast to other publications, parameters like mean pulmonary artery pressure,
specialised centres guarantees a high quality of care, and the regular analysis of the registry data could be an instrument for quality control and might help identify weak points in assessment and treatment of patients affected with a disease leading to marked disabilities and still high mortality.

We thank Ulla Treder (University Hospital of Zurich) and Monika Sorge Maitre (University Hospital of Geneva) for their help with the registry, and Markus Schwerzmann (Cardiology, University Hospital of Berne) for statistical support.

References


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