Epidemiology of pulmonary hypertension: new data from the Swiss registry

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Summary

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

Introduction

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

Abbreviations

CTEPH	chronic thrombotic/embolic pulmonary hypertension
IPAH	idiopathic pulmonary arterial hypertension
NYHA	New York Heart Association
6MWD	6 minute walking distance
PAH	pulmonary arterial hypertension
PAPmean	mean pulmonary artery pressure
PH	pulmonary hypertension
TEA	thrombendarterectomy
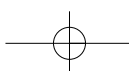
from PH patients from all PH centres and associated hospitals in Switzerland were prospectively collected. In this study, we analyse the epidemiological aspects of these data and focus on basic clinical characteristics of PH patients and estimated burden of the disease in the population.

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, lymphangiomyomatosis, 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 thrombendarterectomy). 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.
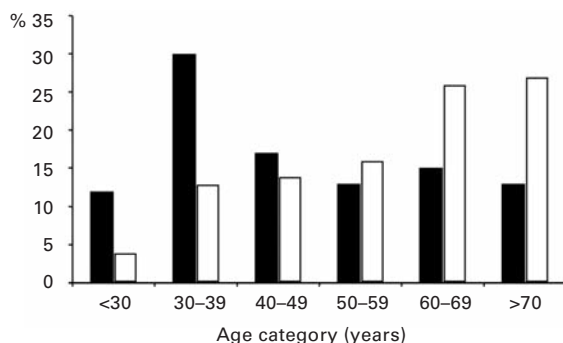
Table 1

	1999	2000	2001	2002	2003	2004	total
Number of patients included	15	36	30	47	63	59	250
Lost of follow-up	2	4	0	4	4	10	24

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.

Figure 1
Age distribution of patients with PH in Switzerland. The black bars show retrospective data from 1991–1999 (from [5]), prospective data from 1999–2004 are in white.

spond 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.

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 re-

Table 2

Characteristics		Total N = 250	IPAH N = 70	CTEPH N = 73	CVD N = 41
Sex (%)	Male	41	36	45	24
	Female	59	64	55	76
Age (%)	<50 y	32	34	16	29
	>50 y	68	66	84	71
NYHA (%)	I	1	0	0	5
	II	12	10	14	15
	III	62	70	57	54
	IV	25	20	29	26
	n	242	69	73	39
6MWD (m)		367 [246–450]	360 [278–428]	389 [270–450]	383 [229–450]
n		215	64	64	31
Mean pulmonary artery pressure (mm Hg)		47 [37–57]	51 [40–64]	46 [37–56]	43 [34–51]
n		176	58	50	27
Pulmonary vascular resistance (dyn.s.cm^{-5})		780 [480–1100]	850 [550–1180]	730 [570–1020]	570 [410–910]
n		159	50	48	23
Mixed venous oxygen saturation (%)		61 [54–67]	62 [57–68]	59 [53–63]	61 [49–69]
n		148	48	44	18
Cardiac output (l/min)		3.9 [3.2–5.0]	4.0 [3.3–5.2]	3.6 [3.0–4.2]	4.1 [3.0–5.3]
n		151	47	47	19
Tricuspid regurgitation pressure gradient (mm Hg)		65 [55–80]	70 [56–84]	70 [56–86]	56 [48–65]
n		189	56	51	33
Responder in vasoreactivity testing (%)		20	35	8	20
n		71	20	24	5

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).
IPAH = idiopathic PAH; CTEPH = chronic thrombo-embolic PH; CVD = PAH associated with collagen vascular disease

Table 3

		Survived N = 150	Died N = 58
Aetiology	IPAH	30%	26%
	CTEPH	31%	24%
	CVD	14%	21%
	other	25%	29%
NYHA class III or IV		86%	98%
Male gender		38%	41%
Responder in vasoreactivity testing		23%	20%
6-minute walking distance (m)		400 [300–459] (134)	273 [174–415] (49)
Systolic blood pressure (mm Hg)		124 [110–139] (148)	120 [110–140] (54)
Mean pulmonary artery pressure (mm Hg)		47 [36–57] (107)	51 [39–55] (37)
Systolic pulmonary artery pressure (mm Hg)		74 [59–90] (101)	79 [63–103] (34)
Pulmonary vascular resistance (dyn.s.cm^{-5})		690 [460–1080] (96)	890 [570–1220] (31)
Cardiac Output (l/min)		4.0 [3.4–5.1] (92)	3.3 [3–5.3] (29)
Mixed venous oxygen saturation (%)		63 [57–68] (88)	56 [50–61] (31)
Right atrial pressure (mm Hg)		7 [4–11] (81)	11 [4–18] (31)
Tricuspid pressure gradient (mm Hg)		62 [54–80] (116)	69 [57–82] (42)
Age at diagnosis (y)		59 [44–69] (150)	60 [44–70] (58)

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

Figure 2

Survival as a function of prognostically important baseline parameters.
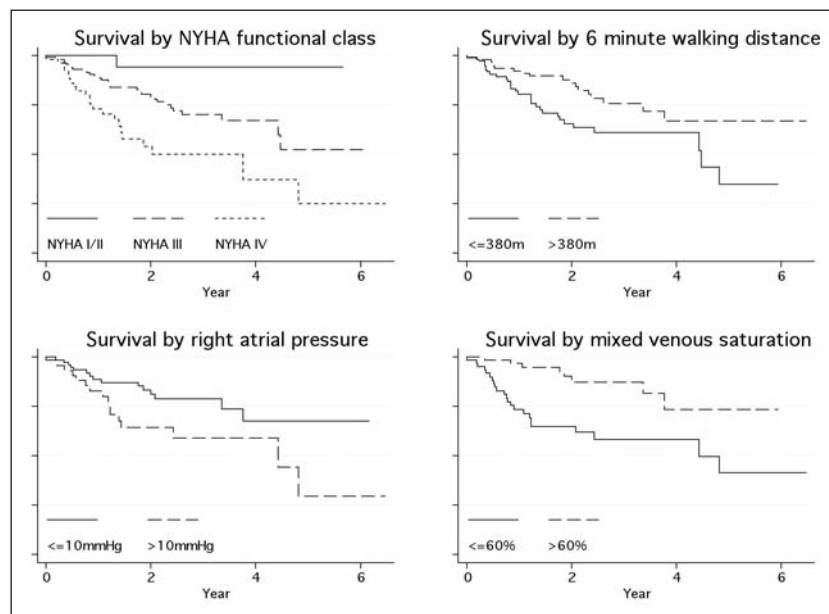
Discussion

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

prevalence of PAH of 26 and of IPAH of 9 per million populations, based on data from the Scottish Pulmonary Vascular Unit. Their data from the national hospitalisation registry showed even higher values (52 and 25 per million, respectively). The conservatively estimated incidence of PAH in Switzerland in 2004 is in the range of the estimation based on the French registry (2.4 cases per one million adult inhabitants) [11], but again lower than the estimated incidence of 7.1 per million in the Scottish population [26]. Further studies from other countries have yet to show which estimates of prevalence and incidence are closest to reality, and whether regional differences play a role. Compared to retrospective data from 1991 to 1999 on PH in Switzerland, the proportion of patients >50 years of age (68%) is now much higher (figure 1) [5]. The reason for this might be the availability of several effective treatments for this disease [1–3] and the increasing clinical experience with those treatments. Physicians therefore consider this disease more often as a potential explanation for exercise intolerance also in elderly patients. The age shift is also due to the higher percentage of patients in the registry with CTEPH (29%) or hypoxaemia-related PH (7%) than documented in the past (15% and 0% respectively) [5]. The increase in the number of patients diagnosed with CTEPH may have been due to a major awareness following the publication of a study showing a more frequent than expected development of PH after acute pulmonary embolism [14].

Our patients are still detected at an advanced stage of the disease, with a mean pulmonary artery pressure of 50 mm Hg and 87% of patients having NYHA class III or IV dyspnoea at diagnosis. Reasons for this late detection might still be an insufficient awareness of the disease and the under-use of echocardiography and diffusion capacity 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 disturbance 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 importance 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 neither a predictor of mortality in this study nor in others [5, 12]. In contrast to other publications, parameters like mean pulmonary artery pressure,

cardiac index, or response to vasoreactivity testing (15–18) could not be identified as significant outcome parameters. Other parameters shown to have prognostic importance such as the presence and size of pericardial effusion on echocardiography [19], blood tests such as plasma brain natriuretic peptide (20), serum cardiac troponin T [21] or hyperuricaemia [22] and quality of life assessments [23] were not routinely collected in this registry.

The lack of prognostic significance of vasoreactivity testing might be due to the small number of patients who had vasoreactivity testing with verified response according to the Venice criteria (n = 71), with only 20 patients having idiopathic pulmonary arterial hypertension. The overall vasoreactivity rate of 20% is in accordance with other data in the literature [24]. However, right heart catheterisation and vasoreactivity testing remain a weak point of the routine assessment of patients with PH in Switzerland. Twenty-eight percent of patients did not undergo right heart catheterisation, and only 71% of patients who had right heart catheterisation for diagnosis had vasoreactivity testing. Whether this is a reporting bias or reflects reality is not known. It could be argued that in patients with CTEPH or PH due to hypoxaemia vasoreactivity, testing is not necessary, as the prognostic value of this manoeuvre has been validated only in patients with pulmonary arterial hypertension. However, vasoreactivity testing was performed in only 57% of patients with idiopathic pulmonary arterial hypertension, but in 44% of patients with CTEPH and 50% of patients with PH due to hypoxaemia or chronic lung disease. The significance of positive vasoreactivity test in the latter patients is not yet clear, but the registry might help to assess this point in the future – provided that right heart catheterisation and vasoreacitivity testing are consequently performed in every patient. As age and co-morbidities of patients with PH increase, the assessment of PH by right heart catheterisation is strongly recommended. It is the only method that reliably excludes left heart insufficiency as a reason for the elevated pulmonary artery pressure; moreover it may correct falsely elevated pressure gradients measured by echocardiography in patients with COPD [25].

In conclusion, the Swiss Registry for Pulmonary Hypertension is a useful and informative tool for clinicians involved in the management of patients with this disease and provides data on epidemiology of PH patients that compares well with data from other registries. A high reporting rate is crucial to have reliable information from the registry and to improve our epidemiological understanding of this disease. It may soon be important to identify patients at an earlier stage of disease to intervene earlier with new therapies. A sustained collaboration between general practitioners and specialised PH centres is necessary in this regard. The management of these patients in

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.

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