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Year: 2001

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## Severe pulmonary hypertension: data from the Swiss Registry

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**Abstract:** **BACKGROUND:** Severe pulmonary hypertension (PH) is a rare disease with a dismal prognosis if untreated. Progress in diagnosis and in the development of effective therapeutic options has created new interest in this pathology. There are, however, only limited data on the prevalence of severe PH unrelated to chronic left ventricular failure or COPD, on the associated conditions and on the parameters with a prognostic impact. With the aid of a retrospective registry we have collected data from 5 centres in Switzerland and attempted to answer the above questions. **METHODS:** Data on patients with PH from 4 university facilities (Zurich, Basle, Geneva and Lausanne) and one well-defined geographical area (Ticino) were retrospectively collected and analysed up to December 1999. Clinical and haemodynamic parameters and associated diseases were noted. We were also interested in the age distribution of the patients and the year of diagnosis of PH. **RESULTS:** We found 106 patients with severe PH (43 men, 63 women, median age 43 years); 79% were in NYHA class III or IV. There was a steep rise in diagnosis of PH after 1995. In 74% PH was either primary or associated with collagen vascular disease or thromboembolic disease. By the end of the observation period 30% of the patients had died. The best distinguishing parameters between surviving patients and those who eventually died were the 6-minute walking test (363 vs. 235 metres,  $p = 0.002$ ), the NYHA class (II vs III/IV,  $p = 0.015$ ), and mixed venous saturation (66.5 vs. 57.9%,  $p = 0.006$ ). Therapy consisted of calcium antagonists in 18% and of (inhaled) prostanoids, chiefly iloprost, in 33%. Seven patients underwent lung transplantation. **CONCLUSIONS:** We conclude that PH is diagnosed more often as diagnostic and therapeutic options improve; that primary forms, and those associated with collagen vascular disease and with chronic venous thromboembolism, make up three-quarters of the aetiologies; and that the 6-minute walking test, the functional class and mixed venous saturation are the best prognostic parameters.

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Journal Article

Published Version

Originally published at:

Stricker, H; Domenighetti, G; Popov, W; Speich, R; Nicod, L; Aubert, J D; Solèr, M (2001). Severe pulmonary hypertension: data from the Swiss Registry. *Swiss Medical Weekly*, 131(23-24):346-350.

# Severe pulmonary hypertension: data from the Swiss Registry

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## Summary

**Background:** Severe pulmonary hypertension (PH) is a rare disease with a dismal prognosis if untreated. Progress in diagnosis and in the development of effective therapeutic options has created new interest in this pathology. There are, however, only limited data on the prevalence of severe PH unrelated to chronic left ventricular failure or COPD, on the associated conditions and on the parameters with a prognostic impact. With the aid of a retrospective registry we have collected data from 5 centres in Switzerland and attempted to answer the above questions.

**Methods:** Data on patients with PH from 4 university facilities (Zurich, Basle, Geneva and Lausanne) and one well-defined geographical area (Ticino) were retrospectively collected and analysed up to December 1999. Clinical and haemodynamic parameters and associated diseases were noted. We were also interested in the age distribution of the patients and the year of diagnosis of PH.

**Results:** We found 106 patients with severe PH (43 men, 63 women, median age 43 years); 79% were in NYHA class III or IV. There was a steep

rise in diagnosis of PH after 1995. In 74% PH was either primary or associated with collagen vascular disease or thromboembolic disease. By the end of the observation period 30% of the patients had died. The best distinguishing parameters between surviving patients and those who eventually died were the 6-minute walking test (363 vs. 235 metres,  $p = 0.002$ ), the NYHA class (II vs III/IV,  $p = 0.015$ ), and mixed venous saturation (66.5 vs. 57.9%,  $p = 0.006$ ). Therapy consisted of calcium antagonists in 18% and of (inhaled) prostanoids, chiefly iloprost, in 33%. Seven patients underwent lung transplantation.

**Conclusions:** We conclude that PH is diagnosed more often as diagnostic and therapeutic options improve; that primary forms, and those associated with collagen vascular disease and with chronic venous thromboembolism, make up three-quarters of the aetiologies; and that the 6-minute walking test, the functional class and mixed venous saturation are the best prognostic parameters.

**Keywords:** pulmonary hypertension; registry; aetiology; prognosis

## Introduction

The apparent rarity of pulmonary hypertension (PH) explains why interest in this disease has long been moderate. It was only in 1973 that a WHO symposium defined its clinical picture, pathology, presumed pathogenesis, diagnosis and treatment, and in 1998 that another WHO conference defined risk factors (such as appetite-suppressing drugs) and medical associations (genetic factors, HIV infection, collagen vascular disease, portal hypertension) which may cause PH [1]. Both improvement of echocardiography as a bed-

side diagnostic tool which has made estimation of pulmonary artery pressure easy, repeatable and reliable [2], and the publication of favourable results regarding exercise tolerance, haemodynamic variables and survival in patients treated with prostanoids has renewed clinical interest in PH [3–6]. It is in this context that the Swiss Registry has been initiated to palliate the paucity of data and probable biases relating to existing data, and to define prognostic parameters associated with life expectancy.

## Material and methods

Data were collected retrospectively from 4 Swiss university centres and Ticino (an area with a well-defined population from the southern part of Switzerland). A small proportion of the data were communicated by individual specialists after a call for patients had been published in the Swiss Medical Bulletin in 1999; these data were reviewed by one of us (GD). The data collected were studied in order to form a picture of the frequency of diagnosis as a function of time and the patients' age at the moment of diagnosis; to assess the conditions associated with PH; to establish a relation between clinical parameters and survival; and to assess the patients' treatment.

PH was defined as mean pulmonary artery pressure >25 mmHg at rest [7]. Secondary causes of PH (not considered in the registry), such as left heart disease with increased pulmonary wedge pressure and obstructive lung disease, were ruled out by cardiac catheterisation and lung function tests. Associated causes of precapillary pul-

monary hypertension were assessed by appropriate means (serological testing for connective tissue diseases and HIV infection, history and imaging for portal hypertension, history for anorectic agents, and cardiac catheterisation for Eisenmenger's syndrome).

Clinical and haemodynamic parameters included NYHA class, 6-minute walking test, cardiac index (CI), mean pulmonary wedge pressure (PWP), systolic (PAP-syst) and mean (PAPmean) pulmonary artery pressure, pulmonary vascular resistance (PVR), mixed venous oxygen saturation (SvO<sub>2</sub>), partial arterial oxygen pressure (PaO<sub>2</sub>) and arterial oxygen saturation (SaO<sub>2</sub>).

The statistical significance ( $p < 0.05$ ) of the parameters between deceased and surviving patients was assessed by two-tailed t-test. The difference in NYHA functional class between these two patient groups was calculated by Fisher's exact test.

## Results

In the period to end-1999 106 patients were retrieved (43 men and 63 women). 10% of patients had a diagnosis of PH before 1990; 4 patients (all surviving) originated from the anorexigen epidemics in the 1960s [8]. Age distribution is shown in figure 1; there is a preponderance of younger patients diagnosed with PH, 63 (59%) being under 50 at the time of diagnosis; the median age was 43. Only 14 out of the 106 patients had been diagnosed before 1990, and we observed a steep rise in the number of cases after 1995 (fig. 2). Table 1 shows the aetiological distribution of PH, with primary PH, PH associated with collagen vascular disease, and chronic thromboembolic PH representing 74% of our patient sample.

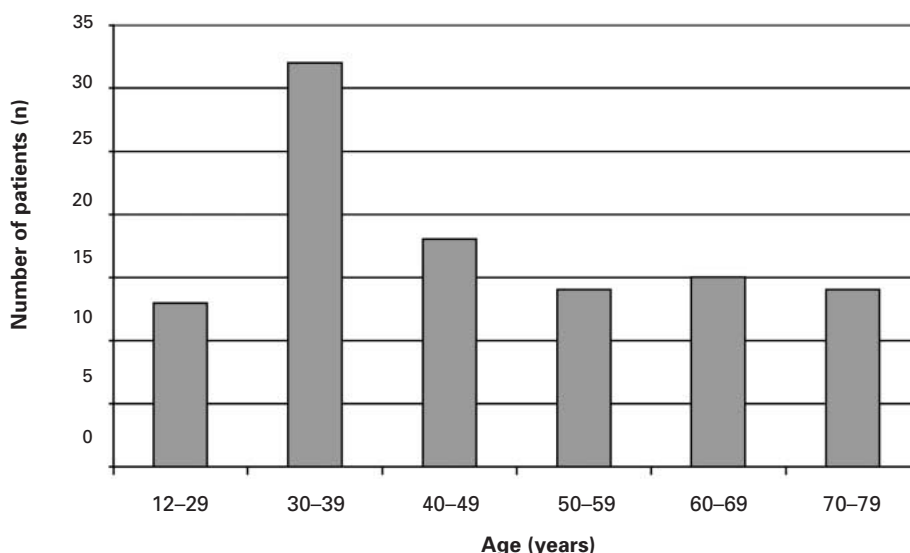
In 17 of our patients (16%) parameters of right heart catheterisation were lacking. These patients were nonetheless included when the history was

consistent with the diagnosis of PH. One patient with collagen vascular disease had died, 15 were alive (3 with primary PH, 1 with thromboembolic PH, 4 with a history of anorexic medication, 3 with collagen vascular disease, and 4 with HIV infection).

Clinically, most patients (79%) were in NYHA class III or IV. 32 (30%) patients had died by the end of 1999. The data of patients with available haemodynamic assessment are shown in Table 2, with a comparison of the parameters in surviving and dead patients. The 6-minute walking test ( $363 \pm 135$  in surviving patients vs.  $235 \pm 155$  m in patients who did not survive;  $p = 0.002$ ), mixed venous oxygen saturation ( $66.5 \pm 9.5$  vs.  $57.9 \pm 10.1\%$ ,  $p = 0.006$ ) and NYHA functional class (2 patients in class II and 30 in class III/IV for patients who did not survive vs 18 in class II and 44 in class

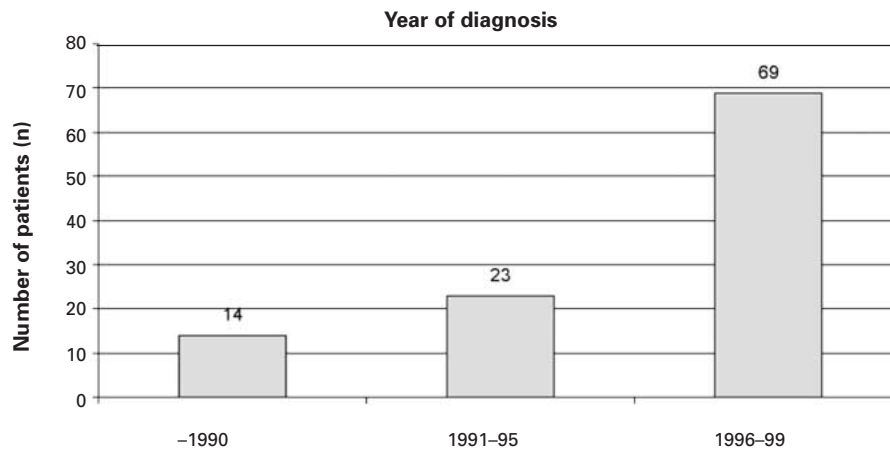
**Figure 1**

Age distribution in patients with PH.



**Figure 2**

Number of patients diagnosed with PH.

**Table 1**

Aetiological distribution in patients with pulmonary hypertension (PH). Comparison between data of United Kingdom (UK) and Switzerland (CH).

	UK (%)	CH (%)
Primary PH	33	37
Venous thromboembolism	13	15
Collagen vascular disease	20	22
Hypoxaemia	4	-
Congenital heart disease	30	4
HIV/anorexic agents/ portal hypertension	-	22

III/IV for surviving patients,  $p = 0.015$ ) best distinguished the two groups, whereas mean or systolic pulmonary artery pressure differed less significantly ( $p = 0.06$  and  $0.05$  respectively); pulmonary vascular resistance did not differ between the two groups.

Nearly two-thirds of the patients (67 out of

106) were anticoagulated, whereas only 19 (18%) were given a calcium antagonist; 6 of these 19 patients (31%) had died (2 of the 6 also inhaled prostacyclin). 35 patients (33%) inhaled epoprostenol or a more stable analogue, iloprost; one of them was later switched to intravenous iloprost because of aggravation of the disease. There were no other patients on intravenous prostacyclin. 26 of the patients under prostanoids (74%) were alive and 9 (26%) had died.

Seven patients underwent lung transplantation (4 with thromboembolic disease, 2 with primary disease and 1 with Eisenmenger's syndrome), 5 of whom are still alive.

A similar number of patients among survivors and those who eventually died were treated with prostanoids or lung transplantation.

**Table 2**

Comparative parameters between dead and surviving patients with PH. SvO<sub>2</sub> = mixed venous oxygen saturation, PAPm = mean pulmonary artery pressure, PAPs = systolic pulmonary artery pressure, PVR = pulmonary vascular resistance, N = number of patients tested.

	N	surviving ( $\times \pm$ SD)	dead ( $\times \pm$ SD)	p
6' walk test (m)	62	363 $\pm$ 135	235 $\pm$ 155	0.002
SvO <sub>2</sub> (%)	66	66.5 $\pm$ 9.5	57.9 $\pm$ 10.1	0.006
PAPm (mm Hg)	82	53 $\pm$ 12	59 $\pm$ 13	0.06
PAPs (mm Hg)	82	81 $\pm$ 19	84 $\pm$ 21	0.05
PVR (dyn.sec.cm-5)	67	892 $\pm$ 419	959 $\pm$ 455	0.11
PaO <sub>2</sub> (kPa)	72	9.1 $\pm$ 1.8	9.2 $\pm$ 2.3	0.9
NYHA class II vs III/IV (n)	94	18 vs 44	2 vs 18	0.015

## Discussion

A classical approach to gaining insight into rare diseases is to establish a registry, which ideally should be based on prospective collection of data according to a standardized protocol [9]. But even a well-designed data collection protocol has its shortcomings: the true incidence of PH may be underestimated even in prospective studies. Data collection centres depend on contributing primary health care providers and primary/secondary facilities, and less awareness of a disease means less re-

ferral of patients to tertiary hospitals. This mechanism may account for the fact that the so far largest prospective data collection on PH from the prospective national registry in the USA, with 32 participating centres, yielded relatively few primary PH patients ( $n = 194$ ) over 4.5 years (1981 to 1985), compared to our 31 patients diagnosed with primary PH within 5 years (1995 to 1999) [10]. A recent publication presented data collected on the basis of death registries; a temporal rise in mortal-

ity was found, which could equally well have been due to better diagnosis as to a real increase in the disease [11]. New registry-based data on PH are, however, lacking.

In recent years the well-established therapy of intravenous prostacyclin for primary pulmonary hypertension [12] has been extended successfully to patients with PH associated with collagen vascular disease [13], HIV infection [14], portal hypertension [15], chronic venous thromboembolism [4] and pulmonary hypertension secondary to congenital heart defects [16]; we therefore included patients with other than primary PH in our registry, in line with a suggestion of Voelkel [17]. The present registry is therefore not directly comparable with former ones which included only patients with primary PH [10]. To our knowledge this is the first registry to enroll patients with severe PH of various aetiologies which eventually result in a common final clinical pathway, i.e. right heart failure.

Our findings show that in 74% of cases pulmonary hypertension unrelated to left heart failure or obstructive lung disease was caused by 3 pathological conditions: the primary form, PH associated with collagen vascular disease, and PH caused by chronic thromboembolic disease.

We confirm a relatively young age at the time of diagnosis (median 43 years), though one that is higher than in other studies [18]; this impression is shared by Lilienfeld and Rubin, whose results suggested that the disease may be more common in the elderly [11]. Older age groups are probably underrepresented in earlier studies: in a data collection published in 1979 the age distribution in patients with primary PH showed a peak incidence between ages 25 and 29, and there were no patients over 60 [19]. One possible explanation is that the unspecific symptoms of PH, such as dyspnea, are falsely attributed to left heart failure, a condition frequently encountered in elderly people. Women were affected more often than men (female to male ratio 1:4, which is slightly lower than the reported ratio of 1:7-3:5). At the time of diagnosis most patients (79%) already presented advanced functional impairment (NYHA class III/IV), which again can be explained by the insidious onset of the disease and the resultant pre-diagnosis delay during which it is unsuspected. Our data show a steep rise in the number of cases diagnosed between 1996 and 1999 compared to those registered between 1991 and 1995. This finding is probably ascribable to better diagnostic tools and not to a higher incidence of the disease, although it is not

possible to draw definite conclusions from our series.

Among the prognostic parameters for survival we found that the 6-minute walking distance, NYHA functional class and mixed venous oxygen saturation distinguished surviving patients from those who would have died better than strictly haemodynamic data such as pulmonary artery pressure or resistance. With the walk test in particular the clinician has a very simple tool for stratifying patients into a high- and a low-risk group. The usefulness of these two parameters has already been mentioned [3, 4].

Classical therapy with vasodilators, digitalis, diuretics, anticoagulants, or oxygen did not alter survival in the study of D'Alonzo [10]. Among our patients relatively few (18%) were given a calcium antagonist, well below the number in the above-cited study where more than 80% received a vasodilator; this may be partly due to our more recent period of data collection, where prostanoid therapy had already been implemented, and reflect the fact that 25% at most of the patients improved under calcium antagonists [20]. Our data, however, are not suitable for drawing conclusions regarding the new vasodilator therapy's positive effects on survival.

Our collection of data on PH has the shortcoming of being retrospective, which may involve inconsistency of data and missing parameters. However, we feel that the present study is representative since it compares well with a British study on the distribution of primary PH and PH associated with other diseases (T. Higenbottam, personal communication); moreover, the present data allowed us to define clinical and haemodynamic parameters which correlated with mortality.

From our retrospectively-collected data on patients with severe PH from 5 centres in Switzerland we conclude that the disease has been more frequently diagnosed in recent years; that the age spectrum of the patients is changing, with a tendency for more elderly people to be diagnosed with PH; and that the easily obtainable 6-minute walking distance, NYHA functional class and mixed venous oxygen saturation are better prognostic parameters than pulmonary artery pressure values.

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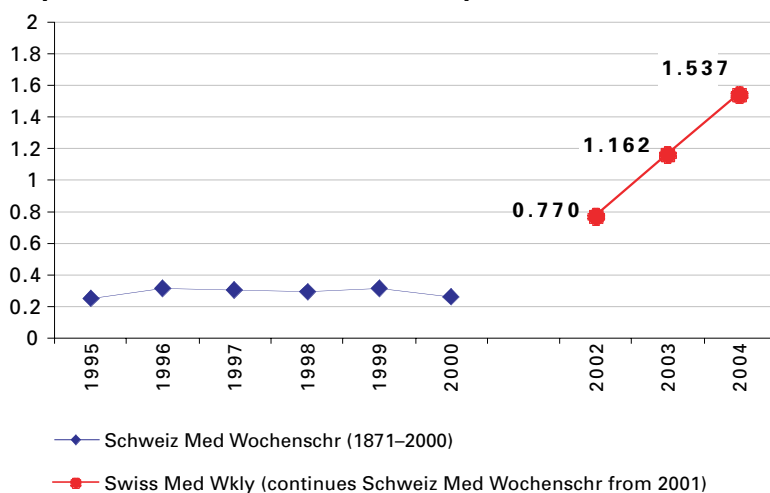
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