Abstract: BACKGROUND: Animal studies and data from a single-center study suggest that tobacco smoke exposure may be a risk factor for precapillary pulmonary hypertension (PH). OBJECTIVE: We aimed to survey tobacco smoke exposure in a large PH collective and to compare it with epidemiological data from healthy subjects. METHODS: This is an international, multicenter, case-control study including patients with pulmonary arterial and chronic thromboembolic PH. All patients were asked specific questions about tobacco smoke exposure. Healthy controls were retrieved from the Swiss Health Survey (n = 18,747). RESULTS: Overall (n = 472), 49% of PH patients were smokers and there was a clear sex difference (women 37%, men 71%). Significantly more PH men were smokers compared with healthy controls, whereas less PH women were ever active smokers. However, 50% of the non-smoking PH women were exposed to secondhand smoke, leading to a significantly higher number of tobacco smoke-exposed individuals compared to healthy controls. PH smokers were significantly younger compared to those not exposed. CONCLUSION: Active and environmental tobacco smoke exposure is common in PH. The higher prevalence of male PH smokers, the higher exposure to environmental tobacco smoke in PH women compared to healthy controls and the lower age at PH diagnosis in smokers may indicate a pathogenic role of tobacco smoke exposure in PH.

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Tobacco Smoke Exposure in Pulmonary Arterial and Thromboembolic Pulmonary Hypertension

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Key Words
Chronic thromboembolic pulmonary hypertension · Pulmonary hypertension · Pulmonary arterial hypertension · Tobacco smoke · Smoking · Risk factor

Abstract
Background: Animal studies and data from a single-center study suggest that tobacco smoke exposure may be a risk factor for precapillary pulmonary hypertension (PH). Objective: We aimed to survey tobacco smoke exposure in a large PH collective and to compare it with epidemiological data from healthy subjects. Methods: This is an international, multicenter, case-control study including patients with pulmonary arterial and chronic thromboembolic PH. All patients were asked specific questions about tobacco smoke exposure. Healthy controls were retrieved from the Swiss Health Survey (n = 18,747). Results: Overall (n = 472), 49% of PH patients were smokers and there was a clear sex difference (women 37%, men 71%). Significantly more PH men were smokers compared with healthy controls, whereas less PH women were ever active smokers. However, 50% of the non-smoking PH women were exposed to secondhand smoke, leading to a significantly higher number of tobacco smoke-exposed individuals compared to healthy controls. PH smokers were significantly younger compared to those not exposed. Conclusion: Active and environmental tobacco smoke exposure is common in PH. The higher prevalence of male PH smokers, the higher exposure to environmental tobacco smoke in PH women compared to healthy controls and the lower age at PH diagnosis in smokers may indicate a pathogenic role of tobacco smoke exposure in PH.

Introduction
Precapillary pulmonary hypertension (PH) has been defined as a mean pulmonary artery pressure (mPAP) ≥25 mm Hg along with a pulmonary artery wedge pres-
sure ≤15 mm Hg (to differentiate from pulmonary venous hypertension due to left heart disease). PH is either idiopathic or associated with many different disorders, such as collagen vascular disease, portal hypertension, hypoxemic lung diseases, chronic thromboembolism and many more [1]. The pathophysiology of PH is still incompletely understood. It is thought that excessive vasoconstriction possibly in combination with inflammation may lead to endothelial dysfunction, which impairs the production of vasodilators along with an overexpression of vasoconstrictors [2]. This imbalance towards vasoconstriction further promotes vascular remodeling. The initial harmful stimulus leading to this deleterious process of endothelial dysfunction and vascular remodeling in PH is still incompletely understood. Possible factors are inflammation, some forms of infection and hypoxia, all most probably on a genetic background of increased susceptibility and aggravated by hitherto unknown environmental risk factors [3]. The penetrance of PH in families with a mutation of the bone morphogenetic protein type II receptor is low and the mutation is seldom found in other forms of PH. Thus, in addition to a genetic predisposition and associated disease, environmental factors may play a pathogenic role. Animal studies have shown that tobacco smoke exposure can lead to pulmonary endothelial dysfunction and plexogenic PH [4, 5], and some reports indicate that this might also be the case in humans [6, 7]. In a single-center study, we recently showed a higher prevalence of smokers (former or current) in patients with pulmonary arterial hypertension (PAH) compared to chronic thromboembolic PH (CTEPH) and healthy controls from the Swiss Health Survey (SHS) 2007 [8]. The present investigation aimed to extend these findings to PH patients in Austria and Germany.

Patients and Methods

This is an international, multicenter, observational, case-control study performed in seven referral centers for PH in Europe. From November 2008 to October 2012, during hospital visits or by telephone calls, patients with precapillary PH were systematically asked questions about their smoking exposure and habits. Patients were divided into smokers (who ever smoked more than 1 packet of cigarettes for over 1 year, ≥1 PY), current smokers and non-smokers. Non-smokers were additionally divided into passive smokers (defined as having been exposed to secondhand smoke for >1 h a day >1 year) and not exposed. Diagnosis of precapillary PH was made according to international criteria and guidelines by a thorough investigation, including right heart catheterization, computed tomography of the chest, a ventilation-perfusion scan, a pulmonary function test, blood gases, blood values and other exams as appropriate [1, 9]. Inclusion criteria were pulmonary artery pressure ≥25 mm Hg and pulmonary artery wedge pressure ≤15 mm Hg. Patients with concomitant chronic lung diseases (WHO group III) and other relevant comorbidities (WHO group V) were excluded from the analysis. Some of the patients recruited in Zürich participated in a first comparable study [8]; they were re-asked during follow-up visits and their data re-analyzed by a different team during the present survey. In addition to tobacco exposure, PH classification and clinical and hemodynamic data were noted and analyzed.

As a control group we used data from 18,747 presumably healthy participants of the SHS performed in 2007. Data retrieval for this survey was by telephone call [8].

Statistical Analysis

The comparison of prevalence rates of smoking exposure between our study population and the controls was performed using the χ² test. Quantitative variable differences in patients and disease characteristics were compared using the Mann-Whitney U test. Smoking exposure differences in subgroups of the study populations were calculated by the χ² test.

Ethics

All patients gave their written informed consent to register their data for scientific purposes and the study was approved by the local ethical authorities of each participating center. It was also registered at ClinicalTrials.gov (NCT01484899).

Results

Patients

Data of 533 precapillary PH patients (62% women, mean age 62 ± 14 years) from Switzerland (42%), Germany (52%) and Austria (6%) were prospectively enrolled. The majority of patients were classified as PAH (64%), from which 60% were idiopathic and 40% were associated PAH. CTEPH was found in 24% of cases. A minority of cases had severe PH associated with chronic lung disease or miscellaneous (8 and 3%, respectively) and were excluded from further analysis due to the known association between tobacco smoke exposure and chronic lung diseases and unknown pathogenesis in miscellaneous forms. The patient characteristics of the 472 patients with PAH or CTEPH are summarized in table 1.

Overall Tobacco Smoke Exposure by Gender

Of these 472 patients with PAH and CTEPH, 233 (49%) were smokers and they demonstrated a clear sex difference (37% of women, 71% of men, p < 0.00001; table 2). Fifty-two (11%) PH patients were persistent smokers (9% of women, 15% of men, p = 0.06). Patients started smoking at an average age of 20 ± 6 years (women 19 ± 4, men 20 ± 8, p = 0.63) and stopped with 43 ± 14 years (women 39 ± 14, men 47 ± 13, p = 0.0001). On average,
PH smokers smoked 22 ± 20 PY (males 28 ± 22, females 16 ± 16, p < 0.0001). From the 239 included PH patients who were not active smokers, 114 (48%) were exposed to secondhand smoke (50% of women, 40% of men, p = 0.22) for an average time of 19 ± 13 years (women 20 ± 12, men 19 ± 17, p = 0.32). Thus, 74% of the PH collective had ever been exposed to tobacco smoke, 49% were active smokers and 24% were exposed to secondhand smoke.

Comparison to Healthy Controls
In comparison to healthy controls, smokers were less frequently found among PH women (37 vs. 43%, p = 0.042) but more frequently found among PH men (71 vs. 57%, p = 0.0007; table 2). Both PH women and men were significantly less persistent smokers compared to the healthy controls (women 9 vs. 24%, p < 0.0001; men 15 vs. 32%, p < 0.0001). However, PH women and men were significantly more frequently exposed to secondhand smoke (women 50 vs. 14%, p < 0.0001; men 40 vs. 27%, p < 0.0001), resulting in a higher overall exposure to tobacco smoke in PH compared with controls (women 68 vs. 51%, p < 0.0001; men 82 vs. 69%, p = 0.0002).

Differential Tobacco Smoke Exposure for PAH and CTEPH
The prevalence of tobacco smoke exposure for PAH and CTEPH is shown in table 3. For both sexes, the percentage of smokers was higher in PAH compared with CTEPH (women 40 vs. 29%, men 75 vs. 64%), but the differences were statistically not significant. A significantly higher percentage of female smokers compared to CTEPH women could only be detected in the group of associated PAH (p = 0.0447).

No significant differences in secondhand smoke exposure were found between non-smoking CTEPH and PAH patients, neither in men nor in women. The age of quitting smoking in PAH women was significantly higher compared to CTEPH women (41 ± 15 vs. 33 ± 11 years, p = 0.0267), whereas in men there was no difference between these groups. CTEPH women were significantly younger at diagnosis of PH than PAH women (45 ± 11 vs. 54 ± 13 years, p = 0.001).

PAH men showed a significantly longer total exposure to tobacco smoke compared to CTEPH men when taking active smoking calculated as cumulative pack years and the duration of passive tobacco smoke exposure together (36 ± 25 vs. 25 ± 21 PY, p = 0.0073). Overall, there seems be a stronger association between tobacco smoke exposure and PAH than CTEPH since the incidence of male smokers in PAH is significantly higher, the incidence of environmental smoke exposure in PAH women is higher, and there seems to be a trend toward a higher incidence of female smokers in PAH compared to CTEPH.

Differential Characteristics for Smokers and Non-Smokers
Smokers among PH women and men were significantly younger compared to those not exposed (women 52 ± 13 vs. 58 ± 18 years, p = 0.0051; men 57 ± 15 vs. 64 ± 17 years, p = 0.0288). Women who smoked were significantly younger at diagnosis than men who smoked (p = 0.0062). Detailed differential characteristics are listed in table 4.

Female smokers had a higher right atrial pressure, and lower mixed venous oxygen saturation and forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) ratio, and males had a lower diffusion capacity for carbon monoxide compared to those not exposed. Women exposed to secondhand smoke had a lower FEV1/FVC compared to...
Tobacco exposure also induced cell proliferation of smooth muscle cells of the vasculature, which was significantly higher compared to healthy controls [10]. PH smokers were significantly younger compared to the non-exposed, and female PH smokers, even though smoking less pack years, were significantly younger than male PH smokers. PAH men showed a significantly higher cumulative tobacco smoke exposure, taking active smoking and environmental smoke exposure together, than CTEPH men.

Since the 1960s it has been known from animal experiments that tobacco smoke inhalation leads to immediate and temporary elevation of the pulmonary arterial pressure. This has been shown in dogs, frogs, rabbits, cats, rats and guinea pigs [11], and animal models of guinea pigs and rats exposed to tobacco smoke were used to study PH and the vasoproliferative response [12, 13]. Our findings of a significantly higher smoking prevalence in PH men and significantly more PH women exposed to tobacco smoke (either active smokers or environmental exposure) may point towards a possible noxious effect of tobacco smoke constituents on the pulmonary vasculature in human beings as well. These noxious stimuli in combination or accumulation with other hits may contribute to pulmonary vasoproliferation and, ultimately, PH. In animal models it could be shown that tobacco smoke inhalation leads to an early elevation of pulmonary arterial pressure, long before destruction of the lung parenchyma [12]. This could also be demonstrated in human studies [7, 14, 15]. Tobacco smoke exposure also induced cell proliferation of smooth muscle cells of the vasculature [13, 16], led to infiltration of inflammatory cells, and gene expression with overproduction of different mediators responsible for cell proliferation and vasomotor regulation, namely inducible nitric oxide synthase [17], endo-

### Table 2. Prevalence and quantity of tobacco smoke exposure

<table>
<thead>
<tr>
<th>Tobacco exposure</th>
<th>Women PH</th>
<th>Odds ratio</th>
<th>Control CH</th>
<th>Odds ratio</th>
<th>Control DE</th>
<th>Control SHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers, n</td>
<td>112 (37)b,c</td>
<td>0.78c</td>
<td>45 (38)b</td>
<td>59 (35)b,c</td>
<td>4,451 (43)</td>
<td>121 (71)b,d</td>
</tr>
<tr>
<td>Persistent smokers, n</td>
<td>27 (9)d</td>
<td>0.32b</td>
<td>11 (9)d</td>
<td>16 (9)d</td>
<td>2,433 (24)</td>
<td>25 (15)d</td>
</tr>
<tr>
<td>Total pack years</td>
<td>16 ± 16b</td>
<td>19 ± 17a</td>
<td>16 ± 15a</td>
<td>–</td>
<td>28 ± 22a</td>
<td>30 ± 24d</td>
</tr>
<tr>
<td>Smoking start age, years</td>
<td>19 ± 4</td>
<td>20 ± 3</td>
<td>19 ± 6</td>
<td>–</td>
<td>20 ± 8</td>
<td>21 ± 7</td>
</tr>
<tr>
<td>Smoking stop age, years</td>
<td>39 ± 14b</td>
<td>41 ± 15a</td>
<td>38 ± 14a</td>
<td>–</td>
<td>47 ± 13b</td>
<td>48 ± 13a</td>
</tr>
<tr>
<td>Age at PH diagnosis, years</td>
<td>56 ± 16</td>
<td>54 ± 17</td>
<td>58 ± 15</td>
<td>–</td>
<td>59 ± 16</td>
<td>57 ± 17</td>
</tr>
<tr>
<td>Overall active and passive tobacco smoke exposure, years</td>
<td>206 (68)b,c</td>
<td>2.10b</td>
<td>83 (71)a,b</td>
<td>111 (66)a,b</td>
<td>5,252 (51)</td>
<td>141 (82)bc</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± SD, or number with percentages in parentheses; values in square brackets are percentages of non-smokers. CH = Switzerland; DE = Germany. Difference between genders: *p < 0.05, **p < 0.001. Difference to Swiss control group SHS: *p < 0.05, **p < 0.001.
Table 3. Tobacco smoke exposure by PH class

<table>
<thead>
<tr>
<th>Tobacco exposure</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAH (n = 232)</td>
<td>PAH (n = 110)</td>
</tr>
<tr>
<td></td>
<td>odds ratio</td>
<td>odds ratio</td>
</tr>
<tr>
<td></td>
<td>(n = 135)</td>
<td>(n = 69)</td>
</tr>
<tr>
<td>Smokers, n</td>
<td>92 (40)</td>
<td>82 (75)</td>
</tr>
<tr>
<td></td>
<td>0.87&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.13&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>1.61&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.65&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Persistent smokers, n</td>
<td>23 (10)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>33 (80)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>0.54&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.03&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total pack years</td>
<td>18 ± 16</td>
<td>17 ± 13</td>
</tr>
<tr>
<td>Smoking start age, years</td>
<td>19 ± 4</td>
<td>19 ± 4</td>
</tr>
<tr>
<td>Smoking stop age, years</td>
<td>41 ± 15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>41 ± 15&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age at PH diagnosis (all subjects: smoker, passive and not exposed)</td>
<td>56 ± 16</td>
<td>57 ± 13</td>
</tr>
<tr>
<td></td>
<td>54 ± 13&lt;sup&gt;a&lt;/sup&gt;</td>
<td>57 ± 13&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Passive smokers</td>
<td>68 (49)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>92 (40)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Exposure to secondhand smoke, years</td>
<td>20 ± 12</td>
<td>21 ± 13</td>
</tr>
<tr>
<td>Overall active and passive tobacco smoke exposure, years</td>
<td>160 (69)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>90 (66)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cumulative active and passive exposure to tobacco smoke, years</td>
<td>24 ± 18</td>
<td>16 ± 19</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± SD, or number with percentages in parentheses; values in square brackets are percentages of non-smokers. IPAH = Idiopathic pulmonary arterial hypertension; APAH = associated pulmonary arterial hypertension; CTEPH = chronic thromboembolic pulmonary hypertension. Difference to CTEPH: <sup>a</sup>p < 0.05. Difference to Swiss control group SHS: <sup>b</sup>p < 0.05; <sup>c</sup>p < 0.001.

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The alterations due to endothelial dysfunction of the pulmonary vasculature, smooth muscle cell function, overexpression of endothelin 1, serotonin, thromboxane A2, nitric oxide, and platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), contribute to the pathogenesis of PH, with endothelial and smooth muscle cell dysfunction being key features of this disease. The altered expression of these factors, particularly PDGF and VEGF, contributes to the development of pulmonary hypertension.
ences to tobacco smoke exposure have been shown for lung cancer [25]. A higher susceptibility could perhaps explain the lower active but higher secondhand smoke exposure in PH women. If predisposed women, for example those who are genetically more susceptible due to alterations in genes responsible for PAH, such as BMPR-2 mutations, are exposed to constituents of tobacco smoke, a lower cumulative dose might be sufficient to initiate pulmonary vascular remodeling, ultimately leading to PH. Potential sex differences in COPD are discussed in the literature [26–28], and it could be shown that PH is more frequent in female COPD patients [29].

In a well-designed recent study, a possible PAH phenotype was characterized which showed worse exercise performance and survival [30]. Characteristics of that phenotype are low diffusing capacity for carbon monoxide (DLCO; <45%), male gender, higher tobacco smoke exposure and slightly lower lung function in terms of FEV₁, FEV₁/FVC and total lung capacity. No correlation to hemodynamic status was seen. Our data is in line with these findings since we found that PH was associated with tobacco smoke exposure in a relevant proportion of patients and we also found slightly lower than predicted lung function values in our collective. However, in contrast, the mean diffusion capacity was not severely reduced in our patients (mean DLCO 62%, 49–77) compared with the depicted subgroup by Trip et al. [30] with a DLCO <45%.

The present study has the following limitations. First, we cannot exclude a selection bias. Although all centers systematically included consecutive PH patients, we cannot exclude that some PH patients were missing in the present analysis due to logistics or for time reasons. Second, as this survey was based on questions regarding tobacco smoke exposure, patients may not have remembered every detail of the amount and timely sequence of tobacco smoke exposure, resulting in a declaration bias of smoking history or exposure to environmental tobacco smoke. However, a similar declaration bias might be found in the healthy controls. We cannot exclude that sick individuals search for a causal explanation for their illness and, thus, their reported smoke exposure might be exaggerated. Third, the mean lung volumes in the present cohort were relatively low (FEV₁ 83 ± 19 and FVC 88 ± 21%) and one could speculate about underlying structural lung disease. However, low lung volumes have been shown for different PH collectives, some with concomitant dynamic hyperinflation mechanical constraints [31, 32]. One could also argue that, consistent with the animal experiments, in some patients after a short exposure time
tobacco smoke exposition leads to changes in the pulmonary vasculature before noticeable destruction of the lung parenchyma, without a progressive increase in pulmonary arterial pressures even after lung destruction becomes manifest [12]. With half of PH patients being smokers, some might have intrinsically smoke-related lung disease with alterations in the pulmonary vessels but not yet in the airways. The fact that PH in COPD characteristically shows mild elevations in pulmonary arterial pressures usually not exceeding 30–35 mm Hg [33, 34] and that in our study 82% of all smokers showed a high mPAP of >35 mm Hg strongly discourages airway disease as being the major cause of PH in our collective. Furthermore, it has to be mentioned that our study includes incident and prevalent cases that cause a lead time bias. Incident cases, presumably showing a phenotype with worse prognosis, may have already disappeared by the time of conducting the study, creating an overweight of prevalent cases with better prognosis and weaker association or sensitivity to tobacco smoke as the offending agent.

In summary, we could herein show that a history of active or environmental tobacco smoke exposure is highly prevalent in PH patients. Supported by experimental data from animal models and evidence of inflammation and endothelial dysfunction in humans as a response to tobacco smoke exposure, these data may indicate that tobacco smoke and its constituents are, among various other factors, involved in the pathogenesis of human PH, perhaps in terms of a second hit to genetically susceptible individuals. These findings are important for PH patients and their caregivers, as early counselling and protection may prevent disease manifestation in relatives or patients at risk.

Conclusion

Tobacco smoke exposure is common in PH: over one third of PH women and two thirds of PH men were active smokers. Strikingly, 10–15% of PH patients are persistent smokers and half of the non-smoking PH women were exposed to secondhand smoke. The higher prevalence of male PH smokers, the significantly higher exposure to environmental tobacco smoke in PH women compared to healthy subjects, and the lower age at PH diagnosis in smokers may indicate that tobacco smoke exposure deteriorates PH, that it might be involved as a second hit in the pathogenesis of PH, and that women may be more susceptible to the constituents of tobacco smoke.

Acknowledgements

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Financial Disclosure and Conflicts of Interest

No conflicts of interests regarding this study are declared by the authors.

References


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