The Effect of Anticoagulant Therapy in Primary and Anorectic Drug-Induced Pulmonary Hypertension*

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In a retrospective study, we tested the hypothesis that anticoagulant therapy with warfarin sodium (Coumadin) has a beneficial influence on the long-term prognosis in patients with primary pulmonary hypertension (PPH) and anorex-induced plexogenic pulmonary hypertension. The study included a total of 173 patients from two European cities. One hundred four of these patients took the anorectic drug aminorex (Menocil), which was available in some European countries almost 30 years ago; 69 patients had pulmonary hypertension of unexplained etiology, ie, PPH. Fifty-six of the 104 aminorex-treated patients and 24 patients in the PPH group received warfarin after diagnosis was established. For analysis, patients were divided into four groups according to their history of aminorex intake and anticoagulant therapy. Survival time, changes in hemodynamics (pulmonary arterial pressure), and improvement in quality of life (scored by the New York Heart Association [NYHA] classification) were compared and analyzed. We found that aminorex-treated patients had a better long-term prognosis than those with PPH (7.5 vs 3.9 years; \( p \leq 0.001 \)). The best mean survival time of 8.3 years was found in anticoagulated aminorex-treated patients, compared to 6.1 years in nonanticoagulated aminorex-treated patients. Moreover, aminorex-treated patients who received anticoagulant therapy soon after the onset of symptoms showed significantly better prognosis (10.9 years) than those who commenced treatment 2 years thereafter (5.9 years) (\( p \leq 0.05 \)). In patients with PPH, systolic pulmonary pressure was shown to influence survival time significantly (\( p \leq 0.0005 \)); however, this correlation was not found in aminorex-treated patients. An improvement of symptoms like dyspnea on exertion was seen in 44.8% of the anticoagulated aminorex-treated patients, while deterioration was evident in 72.2% of the nonanticoagulated aminorex-treated patients. In conclusion, our study has shown that anticoagulant therapy had a positive influence on long-term survival and a significant improvement in quality of life in patients with PPH, in particular in patients with a history of anorectic drug intake.

(CHEST 1997; 112:714-721)

Key words: anticoagulant therapy; drug-induced pulmonary hypertension; exogenous pulmonary hypertension; long-term survival; primary pulmonary hypertension

Abbreviations: NYHA = New York Heart Association; PAPm = mean pulmonary artery pressure; PPH = primary pulmonary hypertension

Both primary pulmonary hypertension (PPH) and exogenous plexogenic pulmonary arteriopathy such as drug-induced pulmonary arteriopathy have an unknown pathophysiologic state, but numerous parallels exist in clinical, functional, and morphologic findings, including the pathogenic mechanism of precapillary vascular obstruction. Since PPH was first described, an impressive array of studies has reported both beneficial and deleterious results of one or another drug. Several studies investigated the efficacy of vasodilator therapy or of anticoagulant treatment in long-term survival or in reduction of pulmonary artery pressure, but the results have always been a subject of controversy. However, a recent study demonstrated that high doses of calcium-channel blockers in patients with PPH who responded with reductions in pulmonary vascular
resistance may improve survival over a 5-year period. The same study has also described that the use of anticoagulant therapy was associated with improved survival, particularly in patients who did not show a decrease in pulmonary artery pressure and pulmonary vascular resistance. Other long-term studies have shown better prognosis among patients with drug-induced pulmonary hypertension; however, to our knowledge, no carefully screened study on the influence of anticoagulant therapy in long-term prognosis of patients with primary or drug-induced pulmonary hypertension has been reported.

Our own experience with prior and preliminary but unpublished data in a patient subgroup has shown a beneficial influence of warfarin sodium (Coumadin) on survival time.

The purpose of this study was to answer the question of beneficial influence of anticoagulant therapy on long-term survival, pulmonary arterial pressure, and changes in quality of life by evaluating the data from 173 patients investigated in Vienna, Austria and Berne, Switzerland. These cities have reported the largest numbers of patients with chronic pulmonary hypertension of vascular origin and unknown etiology in Europe.

**Materials and Methods**

**Patients**

One hundred seventy-three patients (29 men, 144 women) with primary or drug-induced pulmonary hypertension from the Vienna and Berne cardiac centers were studied retrospectively with regard to survival time, changes in pulmonary artery pressure, and quality of life as scored by the New York Heart Association (NYHA) classification. Secondary causes, such as pulmonary embolism, obstructive and restrictive lung disease, intracardial and extracardial shunt lesions, and cardiomypathies were excluded at the time of the diagnosis by means of heart catheterization, chest radiograph and lung perfusion scans, as well as pulmonary angiography in some cases. Criteria for the exclusion of patients with obstructive and/or restrictive lung disease were abnormal results of pulmonary function tests, including body plethysmography, carbon monoxide diffusion capacity, and arterial blood gases. Values were considered abnormal if total lung capacity, vital capacity, FEV1, maximal expiratory flow rate at 50% and 25% of vital capacity, PaO2 and PaCO2, and alveolar-arterial oxygen difference were 20% out of normal range. In addition, there was no evidence that pulmonary hypertension was caused by chronic hypoxemia, sickle cell anemia, or IV drug abuse. None of these patients had evidence of hepatic disease based on liver enzymes or ultrasound testing. In all patients, right heart catheterization with a Swan-Ganz catheter consisted of measurements of right atrial, right ventricular, and pulmonary arterial pressures. Cardiac output was measured by thermodilution and pulmonary vascular resistance was then calculated.

Patients enrolled in this study were divided into four different groups depending on the presence or absence of intake of the anorectic drug aminorex (Menocil), with or without subsequent anticoagulant therapy. No specific patient characteristic was associated with the decision to treat or not treat patients with warfarin. Groups 1 and 2 consisted of patients with a positive history of anorectic drug intake. However, patients in group 1 had been treated with warfarin (Coumadin; Marcoumar) and patients in group 2 had not been treated with this medication. Groups 3 and 4 consisted of patients with PPH who had no history of anorectic drug intake. Of these latter groups, patients treated with warfarin were evaluated in group 3 and those without warfarin medication were evaluated in group 4. Table 1 shows symptoms of patients in the different groups at the time of diagnosis and their treatment.

Survival time was calculated from the time of diagnosis. Changes in quality of life were determined by comparing NYHA categories reported at the time of diagnosis to those reported at the latest evaluation.

**Table 1—Symptoms of the Patients in the Different Groups at the Time of Diagnosis and Their Medical Therapy**

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<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>F/M</th>
<th>Age, Mean</th>
<th>AM</th>
<th>RHF</th>
<th>CYN</th>
<th>Edema</th>
<th>TI</th>
<th>PI</th>
<th>SYNC</th>
<th>NYHA III</th>
<th>NYHA IV</th>
<th>AC</th>
<th>DIG</th>
<th>DIU</th>
<th>ST</th>
<th>ALP</th>
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<td>5</td>
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<td>30</td>
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<td>56</td>
<td>53</td>
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<td>45</td>
<td>36/9</td>
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<td>84</td>
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<td>31</td>
<td>80</td>
<td>152</td>
<td>146</td>
<td>22</td>
<td>12</td>
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</table>

*AM = aminorex; RHF = right heart failure; CYN = cyanosis; TI = tricuspid valve insufficiency; PI = pulmonary valve insufficiency; SYNC = syncope; AC = anticoagulant therapy; DIG = digitalis; DIU = diuretics; ST = steroids; ALP = alpha receptor blockers.

Group 1: Anticoagulated Aminorex-Treated Patients

This group consisted of 56 patients (49 female, 7 male) who took aminorex in the years 1965 to 1969 (mean=1967±0.9) and were treated with warfarin as soon as diagnosis was established. The age of these patients was between 27 and 66 years (mean=47.3 years). The exact number of aminorex tablets taken could be ascertained by 40 patients and was between 10 and 1,400 tablets (mean=192±252).

Symptoms in this group started in the years 1966 to 1971, (mean=1967±1.1) and are listed in Table 1. In all patients, the first right heart catheterization was performed between 1966 and 1978; a second measurement of pulmonary hemodynamics in 21 patients was performed in the years 1970 until 1986. Treatment with warfarin began in 19 patients in the same year of the onset of symptoms, in 19 patients 1 year later, and in nine patients 2 years later.

Group 2: Nonanticoagulated Aminorex-Treated Patients

Group 2 consisted of 48 patients (42 female, 6 male) with a history of aminorex intake during the years 1965 to 1969.
Group 3: Anticoagulated PPH Patients

Twenty-four patients (17 female, 7 male) with PPH were established in this group and had the onset of the disease between 1948 and 1987. At the time of diagnosis, patients’ ages ranged between 13 and 61 years (mean=44±11.7 years). No patient in that group had ever taken amphetamines or anorectic drugs.

All 24 patients had right heart catheterization between 1958 and 1987 (mean=1968). A second measurement of pulmonary hemodynamics could be obtained in only two patients after an average of 7 years (between 1972 and 1978). All patients in that group had anticoagulation with warfarin. In seven patients, treatment with anticoagulation started immediately after diagnosis. In six patients, treatment began in the first year and in four patients it began 2 years after the onset of symptoms.

Group 4: Nonanticoagulated PPH Patients

In group 4, 45 patients (36 female, 9 male) were diagnosed as having PPH, but had neither history of aminorex intake nor treatment with warfarin. Symptoms in that group began between 1953 and 1985 (mean=1971±7.3). A right heart catheterization was performed for all patients in group 4 between 1957 and 1985 (mean=1972). Six patients were investigated a second time between 1972 and 1986. No patients in this group were receiving anticoagulant treatment.

Statistical Analysis

Univariate analysis of survival data was performed using an unpaired Student’s t test or the χ² test. Survival data were analyzed by using the techniques of Kaplan and Meier. Multivariate analysis of prognostic factors was done with use of the Cox stepwise proportional hazards general linear model.

Results

Survival Time

General Remarks: We observed that patients with exogenous pulmonary hypertension, such as aminorex-induced plexogenic pulmonary arteriopathy, had a significant better survival time than patients with idiopathic or PPH, independent of any anticoagulant therapy (7.5±0.6 years vs 3.9±0.5 years; p<0.001). For the entire patient population studied, regardless of whether pulmonary hypertension was exogenous or not, anticoagulation generally showed a significant influence in survival time (7.2±0.6 years vs 4.9±0.6 years; p=0.05).

The survival curve in Figure 1 shows a clearly improved prognosis for aminorex-treated patients who had anticoagulant therapy (group 1) at both the 5-year (63% vs 38%) and 10-year (39% vs 20%) survival points compared with nonanticoagulated patients (group 2). Patients with PPH (groups 3 and 4) showed no difference in the survival curve when treated or not treated with warfarin in the first 5 years after diagnosis. In the following 5 years, a nonsignificant advantage among anticoagulated patients was observed.

Cause of Death: Causes of death were right heart failure in 72% and sudden death in 28% of the patients. None of the anticoagulated patients had side effects of the warfarin therapy or bleeding episodes.

![Figure 1. Kaplan and Meier survival curve for all patients, including 5- and 10-year survival rate.](image-url)
<table>
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<tr>
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<th>No.</th>
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<th>Mean±SD</th>
<th>Range</th>
<th>Mean±SD</th>
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<td>36.8±11.9</td>
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<td>52.0±12.2</td>
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<td>10.0±6.0</td>
<td>37-139</td>
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<td>3-36</td>
<td>16.0±7.2</td>
<td>3-13</td>
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*All pressures given in mm Hg. PAPs=systolic pulmonary artery pressure; PAPd=diastolic PAP; PAPm=mean PAP; RAPm=mean right atrial pressure; RVPs=systolic right ventricular pressure; RVPed=right ventricular end-diastolic pressure; PCWPm=mean pulmonary capillary wedge pressure; CI=cardiac index.
Groups: In group 1, 6 of 56 patients survived 20 years. In this group, the mean survival time was 8.3 (±5.9) years, the longest mean survival time of the groups we studied. Group 2 showed the second longest mean survival time, with an average of 6.1 (±6.3) years. Four of 45 patients survived 20 years. Patients in group 3 had a mean survival time of 4.2 (±4.5) years and none of the patients survived 20 years. Five of 45 patients in group 4 survived to the end of the study; however, in 4 of 5 of these surviving patients, the disease started between 1983 and 1986. Group 4 had the worst mean survival time, with 3.7 (±4.5) years.

A high significance with respect to mean survival time could be found between group 1 and group 3 (p≤0.005). However, no significance was observed in the mean survival time between group 2 and 4, or between groups treated or not treated with warfarin (group 1 vs 2, group 3 vs 4).

Age and Pulmonary Pressure: The age at the time of diagnosis did not influence survival time. However, the severity of systolic pulmonary pressure, evaluated during the first heart catheterization and calculated from patient data, did provide a measure of significant influence (p≤0.0004). In patients with PPH (groups 3 and 4), systolic pulmonary pressure was shown to be significant in terms of survival time (p≤0.0005). However, this factor was not found to be significant in aminorex-treated patients (groups 1 and 2).

Number of Aminorex Tablets: The total amount of aminorex ingested was shown to influence the total survival time (p≤0.01).

Onset of Anticoagulant Therapy: In group 1, early treatment with warfarin significantly improved prognosis. Patients in this group who were placed on a regimen of anticoagulant therapy as soon as symptoms appeared and diagnosis was established (n=19) showed a mean survival time of 10.9 (±5.5) years, compared to 5.9 (±4.5) years for patients (n=9) who were treated with anticoagulant therapy 2 years after the onset of symptoms (p≤0.05). These subgroups showed neither any difference in systolic pulmonary arterial pressure (75±17.9 mm Hg vs 81±21.6 mm Hg) nor in number of ingested aminorex tablets (130±138 vs 143±110). In group 3, however, early anticoagulant therapy appeared to have no statistically significant influence on survival times.

Pulmonary Hemodynamics

General Remarks: Fifty-seven percent of all aminorex-treated patients showed a decrease in pulmonary arterial pressure by the time of the second catheterization. Almost two thirds of these patients were treated with warfarin. For the patients with PPH in group 3 and group 4, hemodynamics improved in two of eight patients (25%).

Groups: In group 1, 21 patients (37%) underwent a second right heart catheterization. An increase in mean pulmonary artery pressure (PAPm) was seen in 7 of the 21 patients, ranging from +9 to +26 mm Hg (mean=+21, SD±5.9), and a decrease was seen in 13 of the 21 patients, ranging from −23 to −3 mm Hg (mean=−8.7, SD±5.8). One patient showed no change in PAPm.

In group 2, a second right heart catheterization was performed in 16 of the 48 patients (33%). Seven of these 16 patients showed an elevation in PAPm that ranged from +2 to +18 mm Hg (mean=+9.5, SD±5.0), while 8 of the 16 showed a decrease in PAPm that ranged from −50 to −1 mm Hg (mean=−19.8, SD±18.6). The PAPm remained unchanged for one patient.

Only 2 of the 24 (8%) patients in group 3 had a second right heart catheterization, with a pressure increase in one patient (+12 mm Hg) and a decrease of −2 mm Hg in another.

In group 4, 6 of the 45 patients (13%) had a second right heart catheterization. Of these six patients, four showed an increase in PAPm ranging from +4 to +42 mm Hg (mean=+15, SD±18.1), one patient remained unchanged, and one had a PAPm drop of −35 mm Hg. Table 2 shows the pulmonary pressure data for all patients in all groups at the first and second catheterization.

In Figure 2, changes of pulmonary hemodynamics are shown during the period of observation for aminorex-treated patients, both those treated and not treated with warfarin. For those who received

![Figure 2. Pulmonary pressure decreases after anticoagulant therapy (group 1: n=21) compared to pulmonary pressure increases with no anticoagulant therapy (group 2: n=16) for aminorex-treated patients.](image-url)
the anticoagulant therapy (group 1), a decrease of pulmonary systolic and mean pressure was noted, while an increase was noted for patients who did not receive the anticoagulant therapy (group 2).

Because only a small number of patients in groups 3 and 4 received a second heart catheterization, no significant changes could be calculated in these groups.

**Anorectic Drug Intake:** The number of aminorex tablets ingested did not affect changes in pulmonary hemodynamics.

**Changes in Quality of Life**

Results of NYHA classifications on quality of life for all patients were compared in regard to the time of diagnosis and the final evaluation. In group 1, NYHA data were available for 49 of 56 patients. Twenty-two of these patients showed improvement in NYHA classification, whereas 18 patients had a deterioration, and 9 patients had unchanged symptoms.

In group 2, NYHA data were available for 18 of 48 patients. Four of the patients in this group showed improvement of symptoms, 13 showed deterioration, and 1 patient showed no change. Data concerning quality of life were determined for 19 of 24 patients in group 3. Five of these patients showed an improvement, 10 a deterioration, and 4 patients unchanged NYHA classification.

Quality of life data were available for 15 of 45 patients in group 4. Two of these patients showed improved conditions, 10 patients showed deteriorated conditions, and 3 patients showed no change in the NYHA classification.

**DISCUSSION**

Pulmonary hypertension is usually secondary to cardiac or pulmonary disease and only rarely is "primary, idiopathic" or "unexplained." **Aminorex fumarate,** which became available as an anorectic drug in three European countries (Germany, Switzerland, Austria), caused an increase in the number of cases of unexplained pulmonary arterial hypertension between 1965 and 1969, also called plexogenic pulmonary arteriopathy.8

Treatment of primary or unexplained pulmonary hypertension remains among the most confounding areas of medicine. Based on their apparently identical pathologic condition and unknown etiology, no difference in therapy exists for primary and aminorex-induced pulmonary hypertension. Patients diagnosed as having either form of disease have been treated only symptomatically with diuretics, digitalis, and various "vasoactive" drugs.

Histologic studies have shown that patients with PPH and patients with aminorex-induced pulmonary hypertension have a broad spectrum of pulmonary vascular changes accompanied by undetected forms of pulmonary thromboembolism, pulmonary veno-occlusive disease, and pulmonary vascular disease. Additionally, these pathologic entities are characterized by changes in pulmonary arterioles.9 Several studies have suggested that thrombosis may play a prominent role in the pathogenesis of PPH.10 Wood11 and Wilcken12 first described patients with signs of obliterative pulmonary hypertension appearing several months after pregnancy. Continuous anticoagulant therapy caused regression of these patients’ signs and symptoms. Fuster et al13 studied patients with PPH and found a statistically significant improvement in survival of 78 patients who had been treated with warfarin, compared to 37 who had received no anticoagulants.4

Independent of any anorectic exposure, patients with anticoagulant therapy showed a better survival time, with the best results in patients with a history of both anorectic drug intake and anticoagulant therapy. However, no significant influence in survival could be found among patients with classical PPH hypertension who were treated with warfarin. Thirty percent of these patients lived for 5 years, and 15% lived for 10 years following diagnosis. Compared to the PPH patients who were not treated with warfarin, those who received anticoagulant therapy appeared to have a slight advantage in survival over the second half of 5 years. Patients who survive 2 to 3 years have an excellent chance of surviving for ≥10 years.14 Also, however, spontaneous reversal of PPH has been reported.15,16

The epidemic of aminorex-induced plexogenic pulmonary arteriopathy has one encouraging feature:10 for some patients, the withdrawal of the provoking stimulus often led to a better prognosis with a symptomatic and hemodynamic improvement in the patient’s condition.17-19 Moreover, the total amount of ingested "aminorex" tablets crucially influenced long-term survival. This important finding implies that the duration of exposure to a provoking stimulus creates greater sensitivity in the vasoconstrictor response of the pulmonary arterial bed and may influence the reversibility of the vasoactive response. Thus, the heterogeneity of pulmonary vascular responses to a certain stimulus could explain why not all patients who ingested aminorex developed more or less severe pulmonary hypertension.20

The importance of early treatment with anticoagulant therapy was also emphasized by our findings. In group 1, the time between the onset of typical signs of pulmonary hypertension and the beginning of anticoagulant therapy played a crucial factor in survival. The earlier the therapy commenced, the better was the long-term survival. This influence was
observed only for patients with aminorex-induced pulmonary hypertension. This may support earlier findings that thrombotic and thromboembolic lesions are occasionally associated with lesions in plexogenic pulmonary arteriopathy.\textsuperscript{10}

High pulmonary vascular resistance and low cardiac output generate slow blood flow in pulmonary arteries and therefore can increase the likelihood of thromboembolic disposition. This likelihood increases with elevated fibrinopeptide A plasma concentrations, reported in patients with PPH, and indicates that thrombin activity is increased.\textsuperscript{31} However, increased fibrinogen plasma levels and a defective fibrinolytic potential in patients with both secondary pulmonary hypertension due to recurrent embolism, like chronic major vessel pulmonary hypertension, and PPH have been reported.\textsuperscript{22} For obvious reasons, therefore, a small pulmonary embolism that might have little effect on normal individuals could have catastrophic consequences for a patient with pulmonary hypertension.\textsuperscript{23}

As reported in earlier publications, age had no influence on survival.\textsuperscript{24} Compared with earlier case reports,\textsuperscript{25} however, we observed an interesting influence of pulmonary pressure on long-term prognosis. For patients with aminorex exposure, the level of systolic pulmonary pressure was not related to survival. However, for patients diagnosed as having PPH, a significant relationship between systolic pulmonary pressure and survival was observed. In one study, higher right arterial pressures, lower cardiac and stroke volume indexes, and higher systemic and pulmonary vascular resistances were reported to influence survival significantly.\textsuperscript{26} In other studies, right ventricular failure that appeared in patients with PPH was followed by a mean survival of <1 year.\textsuperscript{27,28}

Since 1980, when Rubin and Peter\textsuperscript{29} reported a 52\% reduction in pulmonary vascular resistance by treating PPH patients with hydralazine, there have been several studies on the beneficial and adverse effects of vasodilators for PPH.\textsuperscript{30,31} Despite their effectiveness in lowering systemic pressure, vasodilators have not generally produced substantial reductions in pulmonary arterial pressures for patients with PPH.\textsuperscript{32,33} Calcium channel-blocking drugs have shown a reduction in pulmonary artery pressure only in high doses up to 720 mg/d of diltiazem or 240 mg/d of nifedipine, but not in conventional doses.\textsuperscript{3,5}

In our study, aminorex-treated patients were favored with respect to decreases in pulmonary pressure compared to patients with PPH. Sixty-three percent of the aminorex-treated patients were treated with warfarin. The positive results achieved by this treatment repeatedly underscore the likelihood of thrombotic participation in cases of drug-induced pulmonary hypertension,\textsuperscript{10} and the necessity of long-term anticoagulation.\textsuperscript{4,13} Since the number of patients with PPH who received repeated right-sided heart catheterizations was small, no significant influence of anticoagulant treatment on pulmonary pressure changes could be established.

In summary, we found that treatment with warfarin seemed to have some beneficial effects in possibly preventing local thrombosis and in ameliorating pulmonary hypertension and survival,\textsuperscript{34} especially in patients with a history of anorectic intake. However, the mechanism of aminorex-related plexogenic arteriopathy and PPH remains unsolved. Effective treatment strategies for these diseases are not likely until future investigations more clearly define the etiologic mechanisms of plexogenic pulmonary hypertension and PPH.

ACKNOWLEDGMENT: The authors thank Valentin Fuster, MD, and Charles Hales, MD, for their helpful review of this manuscript. We also thank Jo Anne Fordham for proofreading the manuscript and Michael Hiegelsberger, PhD, who produced the graphs for this article.

This article is dedicated to Professor Emeritus Fritz Kaindl, MD, on the occasion on his 75th birthday. At the time of the aminorex epidemic, Professor Kaindl was the first to call in on a symposium to discuss the impact of aminorex on the development of PPH.

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