Parenteral Prostanoid Use at a Tertiary Referral Center

A Retrospective Cohort Study

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BACKGROUND: Evidence-based guidelines recommend the use of parenteral prostaglandin (PP) therapy in patients with advanced pulmonary arterial hypertension (PAH). Despite this, many patients with PAH die without PP therapy. We sought to examine the frequency of PP use at a large referral center and characterize patients with PAH who died without receiving PP.

METHODS: We conducted a single-center retrospective cohort analysis of consecutive patients with PAH between 2008 and 2012. Clinical data and cause of death were compared between patients with PAH treated with PP (PAH-PP) and those who were not but were not documented as poor PP candidates (PAH-nonPP).

RESULTS: Of the 101 patients who received a diagnosis of PAH and died, 61 received PP therapy. Of the 40 patients not treated with PP, 10 did not have documented evaluations for PP therapy (PAH-nonPP) whereas 30 were not considered candidates or refused PP therapy. Compared with PAH-PP, PAH-nonPP had a longer 6-min walk distance, had a longer duration between time of diagnosis and date of worse functional class visit, were less likely to be diagnosed as functional class IV, and had significantly lower right atrial pressure. None of the PAH-nonPP died of progressive PAH.

CONCLUSIONS: We found that most patients who die with PAH are evaluated for PP therapy at a large referral center and the small minority of PAH-nonPP tended to have less severe disease and die of non-PAH-related causes. Our data suggest that at large pulmonary hypertension (PH) centers, the vast majority of patients who are appropriate candidates receive PP therapy.

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ABBREVIATIONS: NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAH-nonPP = patients with pulmonary arterial hypertension not treated with parenteral prostaglandin; PAH-PP = patients with pulmonary arterial hypertension treated with parenteral prostaglandin; PH = pulmonary hypertension; PP = parenteral prostaglandin; REVEAL = Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management; WHO = World Health Organization

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Pulmonary arterial hypertension (PAH) is a progressive disease characterized by pulmonary vascular obliteration that leads to elevated pulmonary vascular resistance and often right heart failure and death.¹⁻³ Although it is rare,^{4,5} PAH is a devastating disease the idiopathic form of which has an estimated median survival of 2.8 years when left untreated.⁶ Modern disease-specific therapy, including phosphodiesterase type 5 inhibitors,^{7,8} endothelin-receptor antagonists,⁹⁻¹² guanylate cyclase agonist,¹³ and prostaglandin analogues,¹⁴⁻¹⁹ have been shown to improve exercise capacity and hemodynamic parameters and are recommended therapy by evidence-based guidelines for treatment of patients with advanced PAH.^{1,20,21} However, previous data have suggested that many patients with PAH die without the benefit of parenteral prostaglandin (PP) therapy.²² The underlying reasons for the lack of PP use in these patients are unknown.

Registry data suggest improved outcomes in PAH in the modern treatment era, yet despite aggressive therapy many patients die either of PAH complications or of other causes that may or may not be related to PAH.²³

In functional class III or IV PAH patients, continuous IV or subcutaneous infusion of prostaglandin continues to be recommended as first-line therapy to prevent PAH-related morbidity and mortality.^{1,24} Yet the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) registry and other recent studies have suggested inconsistent use of these medications, which involve a significant patient burden and frequently are accompanied by moderate to severe side effects in this population.^{22,23} There may be clinical differences not accurately captured by large registries in patients who are treated with PP therapy compared with those who are not.

We sought to examine the frequency of use of PP therapy at a large PAH referral center and characterize patients with PAH who died without receiving this therapy. We hypothesized that patients with PAH who died without being treated with PP therapy were not considered medically appropriate for such therapy or had less severe disease compared with those who were recommended for and accepted PP therapy.

Methods

Patients

We retrospectively reviewed records from all patients treated for PAH at the Vanderbilt Center for Pulmonary Vascular Disease from January 1, 2008 to December 31, 2012 (Vanderbilt University Medical Center institutional review board No. 131250). We included only patients with World Health Organization (WHO) group I PAH who died within the specified time frame. Patients with PH other than WHO group I PAH were excluded. PAH was diagnosed according to standard criteria¹ and medical therapy was at the discretion of the treating physician, in accordance with accepted guidelines.^{1,25} Demographic, echocardiographic, and hemodynamic data were collected, as were date and cause of death. Date of initial diagnosis was recorded as the earliest documentation of PH in the medical record. The date of the worst New York Heart Association (NYHA) functional class and medication regimen at that time were recorded and 6-min walk distance, right heart catheterization, echocardiographic, and other clinical data closest to this visit were used for the purposes of this study to define whether an appropriate clinical event had occurred to recommend prostaglandin therapy. In patients admitted for initiation of PP therapy, this was considered the worst functional class date. We defined PP therapy as IV epoprostenol or treprostinil or subcutaneous treprostinil.

Prostaglandin Group Assignment

Patients were grouped into four categories: (1) those who were deemed candidates for and were treated with PP therapy (PAH-PP), (2) those who did not receive therapy and were documented not to be candidates for PP, (3) those who declined PP therapy but were offered PP therapy, and (4) those who did not receive PP therapy but were not documented either to have declined therapy or to be a poor candidate for PP (PAH-nonPP). Our primary analysis was between the PAH-PP and PAH-nonPP groups. Date of death was identified by the medical record and confirmed by the Social Security Death Index. Cause of death was assessed based on the death certificate if available, or the medical record. A waiver of consent was obtained from the Vanderbilt University Medical Center institutional review board for this study (institutional review board No. 131250).

Statistical Considerations

Data are presented as mean $\pm$ SD unless otherwise noted. Categorical variables were compared using χ^2 or Fisher exact test according to specifications. Mann-Whitney *U* or Kruskal-Wallis test was used to compare differences in groups for continuous variables; χ^2 was used to compare differences in categorical variables. For all analyses, $P < .05$ was considered significant. All statistics were performed using GraphPad Prism (GraphPad Prism version 5 for Mac; GraphPad Software).

Results

Patient Treatment Categories

Overall, 1,786 individuals were seen for PH at our center from January 1, 2008 to December 31, 2012. Of these patients, 368 (20.6%) received a diagnosis of WHO

group I PH (PAH). Of these patients, 101 met criteria for PAH and also died within the specified time frame. [Figure 1](#) shows prostaglandin treatments. Sixty-one patients (60.4%) had a treatment regimen that included PP whereas 40 patients (39.6%) did not. Fifty-four patients received IV epoprostenol, four received

Figure 1 – Patient disposition. Patients with PAH were grouped according to use or not of parenteral prostaglandins (PP). Patients with PAH not treated with PP were further divided between those who were considered for but not offered PP, those who refused PP, and those who neither were documented to be poor candidates nor refused. This last group comprised the PAH-nonPP cohort. FC = functional class; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAH-nonPP = patients with pulmonary arterial hypertension not treated with parenteral prostaglandin; PAH-PP = patients with pulmonary arterial hypertension treated with parenteral prostaglandin.

subcutaneous treprostinil, and three received IV treprostinil. Of the 40 patients not treated with PP, six were offered PP but declined parenteral therapy, 24 were documented in the medical record to have been evaluated or considered for PP therapy but were thought to be poor candidates, and 10 did not have documentation of being considered for PP therapy (PAH-nonPP). In total, 91 of 101 patients (90%) were documented to have been evaluated for PP therapy.

In the 24 patients who were documented to have been evaluated for PP but ultimately were not offered therapy, the reasons were multiple comorbidities (12), preserved cardiac function by right heart catheterization (five), history of inconsistent compliance with medications or follow-up despite attempts to optimize patient adherence (four), and NYHA functional class I or II (three) (Fig 1). The 12 patients with multiple comorbidities included those with metastatic cancer (one), concomitant mild or moderate parenchymal lung disease that was not severe (five), advanced chronic kidney disease or end-stage renal disease (three), debility and/or myopathy (three), complex congenital heart disease (two), and hypertrophic obstructive cardiomyopathy (one). Of the 10 PAH-nonPP, chart review suggested that four were unlikely to have been considered candidates, although they were not documented in the chart owing to a history of noncompliance (one), advanced metastatic malignancy (one), end-stage renal disease (one), and cerebrovascular accident with significant residual deficits (one). This left

six patients who did not have a documented evaluation for PP therapy and also may have been suitable candidates.

Patient Characteristics

Table 1 lists demographic data on the PAH-PP and PAH-nonPP groups. There was no significant difference in age or prevalence of comorbidities such as diabetes, systemic hypertension, or coronary artery disease between the two treatment categories in the cohort. Compared with the PAH-PP, the PAH-nonPP group had fewer women (60% vs 79%; $P = .02$), a lower body mass index (26.2 ± 5.8 vs 31.3 ± 8.8 ; $P = .04$), and a longer 6-min walk distance (336.7 ± 119.6 m vs 214.2 ± 146.0 m; $P < .01$). In addition, PAH-PP had different causes of PAH, such that they were more likely to have heritable and connective tissue disease-associated PAH, whereas PAH-nonPP were more likely to have other forms ($P = .003$): three were associated with congenital heart disease; three had portopulmonary hypertension; and one patient each had connective tissue disease-related PAH, idiopathic pulmonary arterial hypertension, HIV-associated PAH, and mixed (ie, multiple potential PAH causes) PAH. PAH-nonPP also had a longer duration between time of diagnosis and date of worse functional class visit (median, 804 days [95% CI, 383-892 days] vs 301 days [95% CI, 469-1,709 days], $P = .04$), and none were functional class IV compared with almost 30% of the PAH-PP group (18 of 61; $P = .04$). Hemodynamically, the PAH-nonPP group

TABLE 1] Demographics

	PAH-PP (n = 61)	PAH-nonPP (n = 10)	P Value
Age at diagnosis, y	48.0 ± 13.2	44.3 ± 17.6	.53
Sex, number, female	48 (79)	6 (60)	.02
Body mass index, kg/m ²	31.3 ± 8.8	26.2 ± 5.8	.04
PAH type, No. (%)	...	...	.003
Idiopathic or heritable	30 (49)	1 (10)	...
Connective tissue disease	19 (31)	1 (10)	...
Congenital heart disease	4 (7)	3 (30)	...
HIV	1 (2)	1 (10)	...
Other ^a	7 (11)	4 (40)	...
Comorbidities, No. (%)	...	...	...
Diabetes mellitus	12 (20)	1 (10)	.43
Systemic hypertension	26 (43)	2 (20)	.17
Coronary artery disease	8 (13)	0	.22
6-min walk distance, m	214.2 ± 146.0	336.7 ± 119.6	.004
Brain natriuretic peptide, pg/mL	644.9 ± 549.9	680.8 ± 537.3	.84
FEV ₁ , % predicted	67.8 ± 13.1	72.4 ± 17.6	.61
Diffusing capacity of lungs for carbon monoxide, % predicted	60.6 ± 26.3	73.7 ± 24.1	.22
Worst functional class, No. (%)	...	...	.04
III	43	10	...
IV	18	0	...
Duration of disease before worse functional class, median (95% CI), d	301 (383-892)	804 (469-1,709)	.04

All data are shown as mean ± SD unless otherwise noted. PAH = pulmonary arterial hypertension; PAH-nonPP = patients with PAH not treated with parenteral prostaglandin; PAH-PP = patients with PAH treated with parenteral prostaglandin.

^aOther causes of PAH were portopulmonary, hereditary hemorrhagic telangiectasia, pulmonary veno-occlusive disease, distal, univessel chronic thromboembolic PH, and multifactorial.

had significantly lower right atrial pressure (6.1 ± 3.2 vs 12.8 ± 6.0 mm Hg; $P < .001$) (Table 2). Other measurements including pulmonary arterial pressure, pulmonary vascular resistance, pulmonary arterial oxygen saturation, and cardiac index did not differ between groups.

PAH Therapies Used

PAH-nonPP had a higher rate of combination therapy at their worst functional class visit than the PAH-PP group (40% vs 13.3%; $P = .04$). Thirty-three patients from the PAH-PP group (54%) received treatment with PP monotherapy. A higher percentage of PAH-nonPP

TABLE 2] Hemodynamics and Echocardiography

	PAH-PP (n = 61)	PAH-nonPP (n = 10)	P Value
Right atrial pressure, mm Hg	12.8 ± 6.0	6.1 ± 3.2	.0003
Mean pulmonary artery pressure, mm Hg	56.8 ± 9.4	59.8 ± 17.8	.75
Cardiac index, L/min/m ²	2.1 ± 1.0	2.0 ± 0.4	.96
Pulmonary vascular resistance, Wood units	13.1 ± 6.0	13.8 ± 6.3	.71
Pulmonary arterial saturation, %	57.3 ± 9.8	61.4 ± 6.4	.25
Right ventricle function, No. (%)	...	...	.39
Normal or mild dysfunction	7 (11)	1 (10)	...
Moderate dysfunction	15 (25)	3 (30)	...
Severe dysfunction	23 (38)	1 (10)	...
Not specified	15 (24)	5 (50)	...

All data are shown as mean ± SD unless otherwise noted. See Table 1 legend for expansion of abbreviations.

TABLE 3] PAH-Directed Therapy at Worst Functional Class Visit

	PAH-PP (n = 61)	PAH-nonPP (n = 10)	P Value
Phosphodiesterase-5 inhibitor	20 (32)	4 (40)	.15
Endothelin receptor antagonist	15 (25)	7 (70)	.009
Inhaled prostaglandin	0	3 (30)	< .0001
Combination therapy	8 (13)	6 (60)	.04
Investigational drug	0	2 (20)	.002
Therapy naive	34 (56)	2 (20)	.07

All data are presented as No. (%). See Table 1 legend for expansion of abbreviations.

were prescribed endothelin receptor antagonists (70% vs 25%; $P = .009$) or an investigational drug (20% vs 0%; $P = .002$), although the number of patients was very low in this category. There was no statistical difference between groups in use of phosphodiesterase-5 inhibitors (Table 3). PAH-nonPP were more likely to use inhaled prostaglandins (30% vs 0%; $P < .0001$). All patients who were NYHA functional class IV received PP.

Cause of Death

There were no differences in age at death in the PAH-nonPP and PAH-PP groups (49.0 ± 17.7 vs 53.0 ± 12.7 y) or in survival from date of worst functional class (median, 803 days [95% CI, 468-1,709 days] vs 840 days [95% CI, 834-1,411 days]) (Table 4). Most PAH-PP (72%) died as a direct result of PH (sudden death and right heart failure) whereas only 7% of patients died of other causes. Among patients in the PAH-PP group with sudden death, 9 of 16 had a cardiac index < 2 on the

TABLE 4] Causes of Death

	PAH-PP (n = 61)	PAH-nonPP (n = 10)	P Value
Sudden death	16 (26)	5 (50)	.25
Right heart failure	28 (46)	0	.005
Malignancy	0	1 (10)	...
Infection	3 (5)	1 (10)	...
Gastrointestinal hemorrhage	0	2 (20)	...
Dementia	1 (2)	0	...
Unknown	13 (21)	1 (10)	...

All data are presented as No. (%). See Table 1 legend for expansion of abbreviations.

most recent right heart catheterization whereas one of the five PAH-nonPP with sudden death had a cardiac index below this threshold, and this was on a catheterization that was performed 6 years before death. None of the PAH-nonPP had clinical evidence of right heart failure. Conversely, 40% of PAH-nonPP deaths were not directly related to PH. In 13 of 61 of the PAH-PP cohort (21%) and one of 10 of the non-PP cohort (10%), cause of death could not be identified by review of the available medical record. To our knowledge, none of the sudden deaths on PP resulted from interruption of PP, as this is reported to precipitate sudden death.

Discussion

We sought to identify the frequency of death in PAH patients without PP therapy at a large PH referral center, and to understand characteristics distinguishing patients who died without prostaglandin therapy. We found that the great majority of patients (91%) who died were treated with PP or were documented to be either poor candidates, or refused this therapy. Moreover, 60% of the cohort, including all patients with NYHA IV symptoms, received PP therapy, which is similar to the previously reported rate.²² The PAH-nonPP group was characterized by longer duration of disease, less evidence of severe disease, and higher frequency of combination, investigational, or inhaled therapy. In addition, on chart review, four of the 10 PAH patients who died without being offered PP at our center were likely poor candidates owing to medical comorbidities or a history of noncompliance, although this was not documented in the medical record. This left six patients (5.9%) who did not have a documented evaluation for PP therapy but may have been suitable candidates.

PP therapy is considered the reference standard therapy for PAH patients with advanced disease.²⁰ However, recent data from the REVEAL registry has shown that in a large cohort of United States PAH patients, a significant proportion of patients die without the benefit of PP therapy.²² Our results suggest greater use of PP than reported in the REVEAL registry. This may be at least partially because of resources available at large referral centers, such as case management support, familiarity with medication insurance approval, and specifically trained ancillary staff that may not be practical at smaller centers. Because the REVEAL registry includes patients treated at many centers, with different practice patterns and different patient population sizes and characteristics, a deeper understanding of the factors influencing

treatment recommendations, instances of patient refusal, and causes of death in those not treated with prostaglandins is not feasible. Although our data are from a single center, they allow granularity on these previously unanswered questions. We found that at a large referral center, most patients who died had actually been treated with a PP or had been considered for treatment with PP. Almost one quarter of patients were documented to be poor PP therapy candidates, most because of poor compliance or multiple complicating comorbidities that were thought to limit survival or potential to benefit from these therapies. Despite previously published data suggesting improvement in patient compliance when faced with life-threatening situations, the extent of follow-up required for PP therapy and risk of catastrophic adverse events with it in the setting of uncertainty was thought too great to outweigh the potential benefits. In addition, patient preference for not receiving these relatively burdensome therapies accounted for a small percentage of patients who died without PP therapy. These factors of comorbidities and patient preference may account for why some patients died without PP therapy in the REVEAL registry.

Upon more close examination of clinical differences between the PAH-PP and PAH-nonPP cohorts, both groups were similar in both age at diagnosis and age at death, but there were several discrepancies in other characteristics, many of which suggest clinical stability of the non-PP patients. Nearly all of the idiopathic or heritable PAH patients were treated with parenteral therapy whereas the non-PP patients had a more diverse cause of disease and phenotype. In these PAH subtypes, such as portopulmonary hypertension, data on the benefit of prostaglandin therapy are limited if present at all. Patients in the non-PP cohort also had less severe disease as evidenced by lower NYHA functional class, higher 6-min walk distance, and lower mean right atrial pressure. PAH-nonPP were followed in clinic longer before disease worsening and were treated with more combination therapy, including investigational drugs, than those treated with PP therapy. The longer duration of disease and greater use of combination therapy suggest slower disease progression in the PAH-nonPP group. It is possible, however, that traditional markers of poor outcome, such as low 6-min walk distance and right heart failure, do not identify patients at risk of sudden death or other non-PAH-related mortality as successfully in patients followed for over 2 years.

In examining causes of death in the PAH-PP and PAH-nonPP groups, there was a significantly higher percentage of PAH-related deaths (sudden death and right heart failure) in patients treated with PP therapy (72% PAH-related deaths vs 50%). There were no deaths caused by progressive right heart failure in the non-PP patients, which also supports the relative clinical stability and phenotypic difference of this group, or it may suggest difficulty in recognizing patients at risk for sudden death. Patients in the non-PP cohort were more likely to die of causes not directly related to PAH (40% of the cohort died of unrelated causes vs 7% in the PP group), on which prostaglandin therapy would have had little impact. There was a significantly higher frequency of men in the non-PP cohort, which has previously been shown to be an independent risk factor for all cause and sudden death,²⁶ which may have contributed to the higher percentage of sudden death within that group. Overall, our data support the concept that it is frequently difficult to predict death without PP therapy using traditional markers, often because the death is not directly related to PAH.

Limitations to this study include the retrospective, single-center design, which may explain the discrepancy between the use of PP therapy in this study and the REVEAL registry but also may limit the data's generalizability. Although our cohort was well phenotyped, a significant percentage of causes of deaths was unable to be determined as it is often challenging to decipher the cause of death and the contributory role PH had in each clinical scenario. It must also be acknowledged that the decision to recommend PP therapy is subjective and therefore may differ between centers, and the clinical decisions made by the physicians and patients in this center may be different those in from other centers. Finally, for patients in the non-PP group, we cannot determine how PAH complicated treatment in patients who died of non-PAH-related causes.

In conclusion, we found that most patients with advanced PAH who are referred to a tertiary referral center are evaluated for PP therapy. Of those who did not receive therapy, most were evaluated but were documented not to be candidates. Only a small minority of patients died without PP therapy but would otherwise have been considered candidates. These patients tended to be more stable clinically, were followed in clinic longer, and died of causes unrelated to PAH, all of which suggest greater challenges in identifying patients at risk of death outside acute presentation.

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