Causes and Circumstances of Death in Pulmonary Arterial Hypertension

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Rationale: The causes and circumstances surrounding death are understudied in patients with pulmonary arterial hypertension (PAH).

Objectives: We sought to determine the specific reasons and characteristics surrounding the death of patients with PAH.

Methods: All deaths of patients with pulmonary hypertension (PH) followed in the Cleveland Clinic Pulmonary Vascular Program were prospectively reviewed by the PH team. A total of 84 patients with PAH (age 58 ± 14 yr; 73% females) who died between June 2008 and May 2012 were included.

Measurements and Main Results: PH was determined to be the direct cause of death (right heart failure or sudden death) in 37 (44%) patients; PH contributed to but did not directly cause death in 37 (44%) patients; and the death was not related to PH in the remaining cases ($n = 7$; 8.3%). In three (3.6%) patients the final cause of death could not be adequately assessed. Most patients died in a healthcare environment and most received PH-specific therapies. In our cohort, 50% of all patients with PAH and 75.7% of those who died of right heart failure received parenteral prostanoid therapy. Less than half of patients had advanced healthcare directives.

Conclusions: Most patients with PAH in our cohort died of their disease; however, right ventricular failure or sudden death was the sole cause of death in less than half of patients.

Keywords: pulmonary hypertension; outcome assessment; cause of death

Pulmonary hypertension (PH) is a life-threatening condition characterized by a mean pulmonary artery pressure greater than or equal to 25 mm Hg (1, 2). This condition can originate from

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Based on data derived from the National Heart, Lung, and Blood Institute Primary Pulmonary Hypertension Registry, it is believed that most patients with pulmonary arterial hypertension (PAH) die because of progressive right heart failure; however, after significant advances in the diagnosis and treatment of this condition, there is limited understanding of how and why individuals with PAH die.

What This Study Adds to the Field

This study systematically and prospectively evaluates the causes and circumstances of death among a large cohort of patients with PAH in the modern treatment era. Our study shows that PAH was the direct cause of death, or a contributor to death, in 88% of the patients and right ventricular failure or sudden death was the sole cause of death in less than half. Most patients with PAH who died as a result of progressive right heart failure were receiving parenteral prostacyclin analogs at the time of death. In addition, we found that less than half of the patients with PAH had advanced healthcare directives and most individuals died in the healthcare environment, predominantly the intensive care unit.

(Received in original form September 12, 2012; accepted in final form April 5, 2013)

Supported by CTSA KL2 (Grant RR024990 [A.R.T.]) from the National Center for Research Resources, a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. R.A.D. is supported by the following grants: HL081064, HL107147, HL095181, and RR026231 from the NIH; and BRCP 08-049 Third Frontier Program grant from the Ohio Department of Development.

Author Contributions: A.R.T. participated in the design of the study, data collection, classification of patients, statistical analysis, interpretation of the results, writing and critical revision of the manuscript for important intellectual content, and final approval of the manuscript submitted. V.A. participated in the data collection, interpretation of the results, writing of the manuscript and critical revision of the manuscript for important intellectual content, and final approval of the manuscript submitted. O.A.M. generated the idea for the study and participated in the design of it, classification of patients, interpretation of the results, writing and critical revision of the manuscript for important intellectual content, and final approval of the manuscript submitted. J.N. participated in the data collection, writing of the manuscript and critical revision of the manuscript for important intellectual content, and final approval of the manuscript submitted. N.B. participated in the data collection, interpretation of the results, critical revision of the manuscript, and final approval of the manuscript submitted. G.A.H. participated in the classification of patients, interpretation of the results, critical revision of the manuscript for important intellectual content, and final approval of the manuscript submitted. R.A.D. participated in the design of the study, classification of patients, interpretation of the results, writing and critical revision of the manuscript, and final approval of the manuscript submitted.

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Am J Respir Crit Care Med Vol 188, Iss. 3, pp 365–369, Aug 1, 2013

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Originally Published in Press as DOI: 10.1164/rccm.201209-1640OC on April 19, 2013

Internet address: www.atsjournals.org

diverse etiologies that are divided by the Fourth World Symposium (Dana Point, 2008) into five groups (1, 3). Group I PH or pulmonary arterial hypertension (PAH) includes diseases that restrict the pulmonary arterial flow (1). Outcomes vary considerably depending on the cause of PH, its severity, and the availability of treatments (1, 4, 5).

According to the Centers for Disease Control and Prevention–Pulmonary Hypertension Surveillance, 1980–2002, PH has increased as a contributor to death or any hospital diagnosis in recent years, specifically among women and older adults (6). This trend might reflect an increase in physician awareness and changes in screening and reporting this chronic disease (6).

Based on data derived from the NHLBI Primary Pulmonary Hypertension Registry, most patients with PAH died because of progressive right heart failure (7–10); however, after the significant advances in the diagnosis and treatment of this condition, there is limited information on the current causes and modes of death in these individuals (8). This paucity of data stems from several limitations including rarity of the disease, short-term clinical studies, and difficulties in determining the cause of death in ongoing registries. Therefore, there is currently limited understanding of how and why individuals with PAH die.

At our institution, we are in a good position to evaluate the reason and context of death in patients with PAH because we follow a large number of patients with this condition who receive care by a selected team of PH physicians. In addition, all deaths

after June 2008 were reviewed in detail and real time by following an established protocol for quality improvement purposes.

Our study aims are to identify the main conditions that led to the death of patients with PAH in a tertiary care center in the modern era; and to investigate end-of-life context, interventions, and treatment in this patient population. Preliminary results of this study have been previously reported in the form of an abstract (11).

METHODS

This cross-sectional study was approved by the Cleveland Clinic Institutional Review Board (protocol approval number 11-021). Data were thoroughly and prospectively collected initially as part of a quality improvement project and later as an Institutional Review Board approved research study. Informed consent was waived for this study. We included consecutive deceased patients with a diagnosis of PAH confirmed by right heart catheterization (RHC) who were regularly followed in our PH clinic between June 2008 and May 2012. We excluded patients who underwent lung transplantation ($n = 5$). The diagnosis of PH was established using standard criteria (1, 2) and each patient had undergone thorough investigations to identify the cause of PH.

Testing performed on all patients included complete blood count, comprehensive metabolic panel, antinuclear antibody, sedimentation rate, thyroid-stimulating hormone, human immunodeficiency virus serology, pulmonary function tests, 6-minute walk test, chest radiograph, ventilation-perfusion scan, echocardiography, and RHC. We performed further evaluation when tests were either positive or inconclusive. Using these data and at the time of PH diagnosis, two PH physicians (the primary PH physician plus a second unbiased reviewer) determined the cause of PH using the Fourth World symposium in PH classification (3). If disagreement occurred the case was presented to the PH team for consensus. These data were prospectively collected for each patient and recorded in our Pulmonary Hypertension Registry. Registry information on demographics, PH etiology, 6-minute walk test (12), echocardiogram, and RHC were used for the present study. Right ventricular size and function were determined subjectively by experienced cardiologists.

On a weekly basis, the Cleveland Clinic Pulmonary Vascular team reviews all recent deaths in patients with PH as part of our quality improvement program. At least two PH physicians and a PH nurse agree on the likely cause of death in these patients. In addition, the team evaluates the contribution of PH to the death. The contribution of PH is divided as follows: (1) PH was the direct cause of death (progressive right heart failure or sudden death); (2) PH contributed to death (intercurrent illnesses that caused the death, such as pneumonia in a patient with PH); or (3) the cause of death was unrelated to PH (e.g., cancer). To classify the cause of death in these groups we asked ourselves the following questions. Did the patient die of progressive right heart failure or sudden death and would this subject have died from PH even in the absence of a concomitant condition? If the answer to both components of the question was yes, then we classified the death as directly related to PH. Would this patient have died in the absence of PH? If the answer was yes, then we considered the death as unrelated to PH. If the answer was no, then PH contributed to the death. If disagreement exists a third physician reviews the case and a consensus is achieved. This process is followed for all patients with PH that die during hospitalization at the Cleveland Clinic and deceased patients whose information is received from specialty pharmacies, conversations with family members, chart reviews, and querying the National Death Index database.

In our Mortality Review Form we routinely collect the age and date of expiration, date of last admission, date of last clinic visit, place of death, brief medical history, PH-specific diagnosis, comorbidities, date of PH diagnosis, date of start of PH therapy, PH-targeted therapies at the time of death, complications from invasive procedures, and whether there were any potential medical concerns in the care of the patients with PH. In addition, we record all recommendations suggested by the group and the actions taken as a result.

We also reviewed all patients' medical records to supplement the information originally collected. Data obtained included the following: occurrence of syncope or clinical findings of right heart failure (defined

as presence of lower extremity edema, jugular vein distention, right ventricular third heart sound, or hepatomegaly) in the last month of life; New York Heart Association (NYHA) functional class during the last outpatient visit or at the time of last hospitalization (for patients that died in the outpatient or inpatient settings, respectively); initiation of intravenous (IV) prostacyclin analogs in the month before death; reasons for not receiving IV prostacyclin analogs, lung transplant listing, or use of extracorporeal membrane oxygenation; presence of advance directives; use of vasopressors or mechanical ventilation; decision on receiving cardiopulmonary resuscitation (CPR); and choice to withhold active treatments (comfort care) before death. We also recorded the last PH-specific treatment (phosphodiesterase-5 inhibitors, endothelin receptor antagonists, and prostacyclin analogs). We defined PH-specific medications at the time of death as the last medications that the patient was taking before death. In the event that the patient opted for comfort or palliative care, we considered the regimen that the patient was receiving immediately before this decision was made. For all the analyses in this study we only included PH group I patients.

Statistical Analysis

Data are presented as percentages or mean $\pm$ SD when appropriate. Fisher exact test was used for comparison of categorical data. All P values reported are two-tailed. A P value of less than 0.05 was considered significant. The statistical analyses were performed using the statistical package IBM SPSS, version 20 (IBM, Armonk, NY).

RESULTS

Overall Characteristics of the Study Population

Between June 2008 and May 2012, a total of 132 patients with PH died and were reviewed by the PH team. We excluded five patients that had undergone lung transplantation and 43 subjects with non-group I PH (Figure 1). The remaining 84 patients with PAH were included in this study. Mean age $\pm$ SD at the time of death was 58 ± 14 years and 61 (73%) were female. NYHA functional class at the time of last clinic visit was either III or IV in 77 (92%) patients and most of them (93%) had physical findings suggestive of right heart failure. Twenty-nine (35%) of them were on oxygen at an average $\pm$ SD flow of 4 ± 2 L/min. Right ventricular function was either moderately or severely impaired in 71 (84%) patients and 24 (29%) subjects had at least mild pericardial effusion (Table 1).

Causes of Death in Patients with PAH

All patients were reviewed by two physicians and 22 (27%) required a third reviewer to achieve consensus. Specific information regarding the cause of death was available in 81 subjects (96.4%). In three (3.6%) patients the final cause of death could not be adequately assessed. PH was determined to be the direct cause of death (right heart failure or sudden death) in 37 (44%)

Figure 1. Patient inclusion flow chart. PH = pulmonary hypertension.

TABLE 1. PATIENTS' CHARACTERISTICS

	Mean $\pm$ SD or N (%)
N	84
Age at the time of death, yr	58 $\pm$ 14
Female sex (%)	61 (73)
Race (%)	
White	72 (86)
African American	12 (14)
BMI, kg/m ²	30.3 $\pm$ 9
Interval between last clinic visit and death, mo	2.2 (3)
NYHA functional class at last visit	
I	1 (1)
II	6 (7)
III	30 (36)
IV	47 (56)
Right heart failure	78 (93)
Patients on O ₂	29 (35)
O ₂ flow (L/min)	4.1 (2)
D _{LCO} (% of predicted)*	49 $\pm$ 22
Interval between last 6-min walk test and death, mo	7.9 $\pm$ 9
Last 6-min walk test	
Distance walked, m	284 $\pm$ 116
Distance walked % of predicted†	53.4 $\pm$ 19
Interval between last echocardiogram and death, mo	1.5 $\pm$ 3
Echocardiogram	
LVEF, %	57.9 $\pm$ 9
RVSP, mm Hg	82.4 $\pm$ 20
RV function, %	
Normal	9 (11)
Mild	4 (5)
Moderate	16 (19)
Severe	55 (65)
RV dilation, %	
Normal	9 (11)
Mild	5 (6)
Moderate	16 (19)
Severe	54 (64)
Pericardial effusion, %‡	24 (29)
Interval between last RHC and death, yr	2.6 $\pm$ 3
RHC	
RA pressure, mm Hg	12.8 $\pm$ 7
PA mean pressure, mm Hg	51.7 $\pm$ 13
PAOP, mm Hg	12.3 $\pm$ 5
CI, L/min/m ²	2.4 $\pm$ 1
PVR, Wood units	9.7 $\pm$ 5
SvO ₂ , %	62.5 $\pm$ 8

Definition of abbreviations: BMI = body-mass index; BP = blood pressure; CI = cardiac index; D_{LCO} = diffusing capacity of carbon monoxide; eRVSP = estimated RVSP; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PA = pulmonary artery; PAH = pulmonary arterial hypertension; PAOP = pulmonary artery occlusion pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RA = right atrial; RHC = right heart catheterization; RVSP = right ventricular systolic pressure; RV = right ventricular; SvO₂ = mixed venous oxygen saturation.

*Reference equations from Miller and coworkers (16).

†Reference equations from Enright and coworkers (12).

‡Mild or more.

patients. PH contributed but did not directly cause death in 37 (44%) patients and the death was not related to PH in the remaining cases (n = 7; 8.3%). Table 2 shows the PH contribution to death and the diseases that led to demise for all patients with PAH.

Interventions before Death in Patients with PH

Less than half (45%) of patients with PH had advanced health-care directives to specify actions that should be taken regarding their health in the event they cannot make decisions. CPR and mechanical ventilation were provided to 22 (31%) and 33 (40%) patients before death, respectively. All patients in NYHA functional class III–IV were considered for transplantation. Few

patients met criteria or desire to be listed for lung transplantation, predominantly because of comorbidities or advanced age (Figure 2). A small percentage of subjects with PAH (n = 11; 13%) were started on IV prostacyclin analogs the month before death (Table 3).

Treatment before Death

A total of 42 (50%) patients with PAH received parenteral prostacyclin analogs before death (38% were in NYHA class III and 62% in class IV; *see* Table 4). Patients who died of right heart failure more commonly received parenteral prostacyclin analogs than individuals who died of conditions other than right heart failure (75.7% vs. 31.8%; *P* < 0.001). Figure 2 shows the number (percentage) of patients receiving prostacyclin analogs and reasons for not receiving this treatment in those that died of right heart failure.

Place of Death

Place of death was determined in 81 patients with PAH and most of these individuals died in a healthcare environment (n = 65; 80%), predominantly in the intensive care unit (ICU) (n = 42; 52%). A few patients died in palliative care units (n = 7; 8.6%). Of the patients that died in a healthcare setting and were not on palliative care units (n = 58), 45 (78%) died at the Cleveland Clinic and 13 (22%) at outside hospitals (Table 5).

DISCUSSION

This is one of the few studies to systematically and prospectively evaluate the causes and circumstances of death among a large cohort of patients with PAH in the modern treatment era. Our study shows that in PH group I, PH was the direct cause or contributed to death in 88% of the patients, and progressive right heart failure or sudden death was the specific cause of death in 44% of them. Most patients with PAH that died as a result of progressive right heart failure were receiving parenteral prostacyclin analogs at the time of death. Less than half of the patients with PAH had advanced healthcare directives and most individuals died in the healthcare environment, predominantly the ICU.

TABLE 2. CAUSES OF DEATH

	N (%)
N	84
PH contribution to death	
Death directly related to PH	37 (44)
PH contributed to death	37 (44)
PH was not related to death	7 (8.3)
Missing	3 (3.6)
Specific causes of death	
Right heart failure/sudden death	37 (44)
Respiratory (non-PH)	14 (16.7)
Pulmonary embolism	0 (0)
Severe sepsis/septic shock	6 (7.1)
Acute renal failure	5 (6.0)
Cardiovascular	7 (8.3)
Neoplasia	8 (9.5)
Miscellaneous	3 (3.6)
Missing	4 (4.8)

Definition of abbreviation: PH = pulmonary hypertension.

Respiratory diseases included progressive interstitial lung disease, chronic obstructive pulmonary disease, and pneumonia. Cardiovascular causes encompassed acute myocardial infarction, cardiomyopathy, cardiogenic shock, and endocarditis. Neoplasia comprised lung cancer, breast cancer, renal cancer, large cell lymphoma, and melanoma. Miscellaneous causes consisted of gastrointestinal bleeding, peritonitis, stroke, and perioperative complications.

Figure 2. Treatments provided to patients with pulmonary arterial hypertension (PAH) that died of worsening pulmonary hypertension (PH). *Number of patients is 81 because we excluded three patients with undetermined cause of death. All these patients received PH-specific therapies. ¶Comorbidities include renal failure; cirrhosis; schizophrenia; coronary artery disease; bacteremia; and chronic gastrointestinal bleeding (arteriovenous malformation). Values are presented as n (%). ILD = interstitial lung disease; IV = intravenous; NYHA = New York Heart Association; P = patients; SQ = subcutaneous; Tx = treatment.

Limited data exist concerning the causes of death in patients with PAH in the literature in part because of the difficulties in accurately identifying the specific reason for the patient's demise. This complexity is reflected in our study by need of a third reviewer to achieve consensus in approximately a quarter of our patients with PAH. Even though PH contributed to death in most of our patients we found that progressive right ventricular failure or sudden death was the sole cause of death in a smaller group of patients (44%). The Patient Registry for the Characterization of Primary Pulmonary Hypertension by the NHLBI reported in 1991 the cause of death in 106 patients with idiopathic PAH, before the availability of PH-specific therapies (7). In this multicenter registry, causes of death were right ventricular failure or sudden death in 73% and others in 27% (medications adverse effects, surgery, pneumonia, and cerebrovascular accidents) (7). Similarly, a retrospective nationwide survey in Japan between the years 1980 and 1990 (139 deaths) revealed that in 84.2% of the patients death was considered to be related to PH. In a recent study, focused on the emergency treatments for PAH, the reported causes of death were right ventricular failure or sudden death in 50%, and a variety of other causes in the other half of the patients (8).

TABLE 3. INTERVENTIONS BEFORE DEATH IN PATIENTS WITH PH

	Number of Patients with Information Available	N (%)
Advanced directives	73	33 (45)
DNR	83	45 (54)
CPR	71	22 (31)
Comfort care	82	42 (51)
Mechanical ventilation	83	33 (40)
IV prostacyclin analogs initiation*	84	11 (13)
Vasopressors	69	35 (51)
ECMO	84	1 (1)
Lung transplant listing	84	2 (2)

Definition of abbreviations: CPR = cardiopulmonary resuscitation; DNR = do not resuscitate; ECMO = extracorporeal membrane oxygenation; IV = intravenous.

Percentages vary due to missing data.

*Initiation of intravenous prostacyclin analogs the month before death.

Preliminary reports from the REVEAL registry have suggested under-treatment of patients with PAH either when they progress from NYHA functional class III to class IV or before death (13, 14). These findings suggest that a large proportion of patients who could have benefited from parenteral therapy or a combination of PH-specific therapies did not receive them (13, 14). We investigated this hypothesis in our cohort of patients and found that this is not the case in our center. In our cohort, all but one patient received some form of PH-specific therapy and more than half of them (57.2%) were on dual or triple combination therapy at the time of death. Seventy percent of patients with PAH that died of right heart failure received parenteral prostanoid therapy. The 30% of patients who did not receive parenteral prostanoids had valid reasons for this decision, such as refusal of parenteral therapy or being poor candidates for this therapy. Based on our findings, it is the view of the authors that most patients that are appropriate candidates for parenteral prostanoid therapy are receiving this treatment at our institution.

Another interesting finding of our study is that overall, 44% of patients with PAH who died were NYHA class I–III at their last visit before death. Even among patients with PH group I in whom PH was directly responsible for their death, fully 38% of patients were in NYHA I–III at their last clinic visit. This may be another reason why some patients with PH are not treated with parenteral therapies before death and highlights the importance of close follow-up.

Lung transplantation remains an important treatment option for patients with advanced PAH (15). In our practice, all

TABLE 4. MEDICATIONS BEFORE DEATH

Medications	Mean ± SD or N (%)
N	84
Class of PH-specific therapies	
PDE-5 inhibitors	63 (75)
ERA	33 (39)
Inhaled prostacyclin analogs	8 (10)
IV or SQ prostacyclin analogs	42 (50)
Combination of PH-specific therapies	
No PH therapies	1 (1.2)
Single PH therapy	35 (41.7)
Dual PH therapy	35 (41.7)
Triple PH therapy	13 (15.5)
Number of PH therapies	1.7 ± 0.7

Definition of abbreviations: ERA = endothelin receptor antagonist; IV = intravenous; PDE-5 = phosphodiesterase-5; PH = pulmonary hypertension; SQ = subcutaneous.

Table 5. PLACE OF DEATH OF PATIENTS WITH PH

Place of Death	N (%)
N	81*
Out of the hospital	16 (19.8)
RNF, SNF, ER, OR	16 (19.8)
ICU	42 (51.9)
Palliative care	7 (8.6)
Place of inpatient deaths†	
Cleveland Clinic	45 (78)
Outside hospital	13 (22)

Definition of abbreviations: ER = emergency room; ICU = intensive care unit; OR = operating room; RNF = regular nursing floor; SNF = skilled nursing facility.

* Information on the place of death was not available in three patients with PAH.

† Not including palliative care.

patients with PAH in NYHA class III–IV are considered for transplantation; however, in our cohort only four patients who died of right heart failure or sudden death were listed for lung transplantation. Other patients were evaluated and believed not to be suitable lung transplant candidates, largely because of the presence of comorbidities or advanced age. This finding suggests that modern PH therapies delayed transplant evaluation to later stages in life, which are associated with an increased number of comorbidities that could render patients not ideal candidates for transplantation.

An important aspect of our study is that less than half of patients with PAH (45%) had advanced healthcare directives, a lower than ideal percentage in a population with a severe and ultimately fatal disease. CPR and mechanical ventilation were provided to about a third of patients and vasopressors in half of them despite unproved beneficial effect in this population. A retrospective multicenter study on the frequency and results of CPR in PAH showed that CPR was attempted in 26% of these patients who had circulatory arrest, mostly in healthcare settings and the medical ICU, and only 6% of those in whom CPR was attempted survived more than 3 months (10). These findings suggest that a more proactive approach that includes talking about end-of-life decisions may be required in this patient population.

Strengths of this study are (1) rigorous prospective evaluation of patients, (2) meticulous review of information regarding cause and mode of death by PH specialists, and (3) all patients had diagnosis of PAH by RHC. Limitations of our study warrant comment. Because the study group consisted of patients seen at a single tertiary care center with a large PH program, the results might not be generalizable to other centers. It may be difficult to completely explain the differences between our findings and those of the NHLBI registry and Japanese survey because they may simply be a reflection of modern demographics. Also, these results do not apply to PH groups other than group I. A multicenter and prospective study is important to confirm our findings.

Conclusions

In most patients with PAH in our cohort, the disease contributed to their death. Right ventricular failure or sudden death was the sole cause of death in less than half. Most of the patients with PAH received PH-specific therapies and died in a healthcare setting, predominantly medical ICU.

Author disclosures are available with the text of this article at www.atsjournals.org.

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