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Syncope in Adults With Pulmonary Arterial Hypertension

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Objectives The aim of this study was to determine the prognostic significance of syncope in pulmonary arterial hypertension (PAH).

Background Some patients with PAH have a history of syncope at presentation. The prognostic implications of syncope in PAH have not yet been well characterized.

Methods This was a single-center cohort study of 378 patients with PAH seen at a dedicated pulmonary hypertension clinic over an 8-year period. All patients completed a standardized symptom assessment at the time of diagnosis.

Results Forty-five (12%) patients had a history of syncope at the time of PAH diagnosis. There were no significant differences in sex, age, functional class, 6-min walk distance, or etiology of PAH in syncopal versus nonsyncopal patients. Syncopal patients presented with higher right atrial pressure and lower cardiac outputs with lower survival rates (1-, 3-, and 5-year rates): 69% (95% confidence interval [CI]: 54% to 81%); 51% (95% CI: 36% to 65%); and 37% (95% CI: 24% to 53%), respectively, compared with 82% (95% CI: 77% to 86%); 64% (95% CI: 64% to 69%); and 54% (95% CI: 48% to 59%), respectively, in nonsyncopal patients. Syncope was a significant predictor of mortality (hazard ratio: 1.94, 95% CI: 1.20 to 2.99), after adjusting for age, sex, functional class, 6-min walk distance, diffusing capacity of carbon monoxide, and right atrial pressure. Syncopal patients had similarly poor outcomes compared with nonsyncopal patients presenting with class 4 symptoms.

Conclusions Syncope in PAH is associated with worsening right heart function and is an independent predictor of a poor prognosis. (J Am Coll Cardiol 2011;58:863–7) © 2011 by the American College of Cardiology Foundation

Pulmonary arterial hypertension (PAH) is a devastating illness of pulmonary vascular remodeling and right heart failure, with the clinical presentation typically characterized by exertional dyspnea (1). A subset of adult PAH patients present with syncope (1,2). Historical data from the National Prospective Study in PAH from 1981 to 1985 suggested the incidence of syncope on referral to a PAH center was as high as 36% (3). Clinical experience suggests that, despite limited data, this might be an exaggerated figure and not consistent with current findings.

Experts consider syncope to confer a poor prognosis in PAH (4). At the second World Symposium on PAH in 1998, the New York Heart Association (NYHA) functional classification (FC) of dyspnea was adapted to reflect PAH pathophysiology (5) with incorporation of pre-syncope in determining PAH disease severity. This World Health Organization classification has been retained in some consensus documents (6,7), whereas others have tended to emphasize the NYHA FC system (8), reflecting uncertainty about the role of pre-syncope in estimating disease severity. Although many practicing PAH physicians equate syncope (i.e., the severe end of the pre-syncope spectrum) to FC 4 status, no expert panel has stated specifically how syncope should affect FC of the disease. Limited published data support the perceived negative connotation of syncope in PAH.

The purpose of the present study was to determine the prevalence of syncope in newly diagnosed patients with PAH and to characterize its clinical, hemodynamic, and prognostic significance.

Methods

Study sample. We studied all consecutive adults (age ≥18 years) with PAH, included from the date of their first visit confirming the diagnosis of PAH at the Mayo Clinic Rochester Pulmonary Hypertension Clinic between January

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Abbreviations and Acronyms

6MW = 6-min walk
CI = confidence interval
FC = functional class/classification
HR = hazard ratio
NYHA = New York Heart Association
PAH = pulmonary arterial hypertension
RA = right atrial
RV = right ventricle/ventricular

1, 1998 and December 31, 2005. Patients already receiving "PH specific therapy" were excluded. Data entry occurred after the complete initial evaluation. For the purposes of this study, patients were included if they: 1) met criteria for the diagnosis of Group 1 PH, with a mean pulmonary arterial pressure ≥25 mm Hg, as defined by expert consensus (8); and 2) completed a standardized symptom questionnaire. Etiology of PAH was designated as idiopathic, familial, or anorexigenic; associated with connective tissue disease; or other PAH. Of 462 patients with group 1 PH, 84 were excluded because a standardized symptom questionnaire was not completed at the time of their initial evaluation. The remaining 378 patients comprised the study population.

Syncope. Syncope was determined on the basis of the results of the standardized symptom questionnaire performed at initial PAH evaluation with a positive answer to this question (with 2 minor modifications over the study period with subsequent questionnaire updates): 1) "Have you 'blacked out' or lost consciousness during recent months"; 2) "Have you 'blacked out' or lost consciousness in the past few months"; or 3) "Have you recently had 'blackouts' or loss of consciousness that you wish to call to the attention of your health care provider?" Additional queries included dizziness and light-headedness.

Patient characteristics and testing. We analyzed the following baseline characteristics at the time of referral: age; sex; NYHA dyspnea/fatigue FC; 6-min walk (6MW) distance; hemoglobin; estimated glomerular filtration rate (9); B-type natriuretic peptide; and diffusing capacity of carbon monoxide on pulmonary function testing, expressed as a percentage of age, sex, race, and height-adjusted normal. The 6MW test was performed under standard conditions, supervised by a PH clinic nurse, and on current oxygen prescription (if relevant). In addition to distance, standing blood pressure, heart rate, and pulse oximetry were assessed immediately before and after the walk.

Transthoracic echocardiography was performed according to contemporary American Society of Echocardiography guidelines (10). Right ventricular (RV) systolic pressure was determined as: $4 \times (\text{peak trans-tricuspid valve systolic regurgitant velocity})^2$ + estimated right atrial (RA) pressure (on the basis of 2-dimensional and Doppler characteristics of the inferior vena cava and hepatic veins). The severity of RA and RV enlargement, RV systolic dysfunction, tricuspid valve regurgitation, and the presence of a pericardial effusion were scored on an ordinal qualitative scale on the basis of visual assessment by an experienced echocardiologist (normal or mild, moderate, severe). The RV index of myocardial performance (Tei index), an integrative measure of both RV systolic and diastolic function, was reported separately (11). Parameters of mean pulmonary arterial pressure, RA pressure, pulmonary vascular resistance, and cardiac output by thermodilution were recorded at the time of right heart catheterization.

Vital status was available in all patients as of June 30, 2009. Vital status was censored at 5 years if follow-up was longer. In those patients who received a lung (n = 3), heart/lung (n = 5), or liver (n = 3) transplant, follow-up was ended at the date of transplantation. Mayo medical records provided vital status for 92% of subjects; the remaining 8% were obtained from the National Death Index. When available, the cause of death was assessed as: 1) "unexpected or sudden death" whether witnessed or unwitnessed; 2) "primarily PAH related," referring to death occurring in the setting of progressive symptoms and signs of PAH and right heart failure; 3) "secondarily associated with PAH" when death occurred with PAH complicated by an alternate acute illness (e.g., pneumonia) and PAH was likely a major contributor to death; or 4) "other-not PAH related." All patients agreed to the use of their medical information for research purposes (on the basis of their Minnesota Research Authorization), and the study was approved by the institutional review board.

Statistical analyses. Statistical analyses were performed with JMP (version 8.0, SAS Institute, Inc., Cary, North Carolina). Continuous variables are presented as mean ± SD or median with interquartile range and tested between groups with analysis of variance or Mann-Whitney comparison (if not normally distributed). Categorical variables were presented as number and percentage, and comparisons were done with Pearson chi-square analysis.

Cox proportional hazards regression models were used to identify correlates of mortality. Results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Models were developed with stepwise techniques with consideration of clinically relevant variables with $p < 0.1$ in the univariate analysis. These included age, sex, syncope, FC, etiology of PAH, 6MW distance, glomerular filtration rate, diffusing capacity of carbon monoxide, RV enlargement, estimated RA pressure, mean pulmonary arterial pressure, and cardiac index. Variables were retained in the model with a $p < 0.1$. For patients in whom data was incomplete, additional categorical variables (test done, test not done) were included. Long-term follow-up of patients is presented on the basis of the Kaplan-Meier product-limit method and compared between groups with the log-rank test. For all analyses, $p < 0.05$ was considered to be significant.

Results

Clinical characteristics. The characteristics of the 378 subjects with PAH are given in Table 1. At the time of presentation, 45 (11.9%) patients reported a recent history

Table 1 Characteristics of Study Patients With and Without Syncope

	Syncope (n = 45)	No Syncope (n = 333)	p Value
Clinical characteristics			
Female	71	75	0.60
Age, yrs	56 ± 16	54 ± 15	0.44
Symptom duration, yrs	1.6 ± 1.7	1.9 ± 2	0.42
Body mass index, kg/m^2	28.5 ± 6	28.6 ± 7	0.90
NYHA functional class I to II	33	32	—
NYHA functional class III	58	54	0.60*
NYHA functional class IV	9	14	—
6MW distance, m	331 ± 121	320 ± 128	0.63
Serum hemoglobin, mg/dl	14 ± 3	14 ± 2	0.53
GFR, per 10 cc/min/1.72 m^2 decline	57 ± 18	60 ± 19	0.24
Mean BNP (n = 12, n = 120)	399 ± 315	291 ± 337	0.29
Mean DLCO, %	52 ± 20	61 ± 23	0.06
PAH etiology			
Idiopathic and familial PAH	48	55	
PAH with collagen vascular disease	30	24	0.60*
Other group 1 PH	23	21	
Echocardiographic data			
Severe RA enlargement	33	25	0.12
Severe RV enlargement	49	39	0.10
Severe tricuspid valve regurgitation	9	9	0.96
RV index of myocardial performance	0.69 ± 0.3	0.64 ± 0.3	0.29
Estimated RA pressure, mm Hg	15 ± 4	13 ± 5	0.05
Presence of pericardial effusion	38	24	0.04
RV systolic pressure, mm Hg	86 ± 24	84 ± 24	0.56
Left ventricular ejection fraction, %	62 ± 11	63 ± 8	0.44
Right heart catheterization			
Mean PA pressure, mm Hg	51 ± 11	51 ± 13	0.94
RA pressure, mm Hg	15 ± 6	12 ± 6	0.01
Cardiac output, l/min	4.1 ± 1.2	5.0 ± 1.9	0.01
Cardiac index, l/min/m^2	2.2 ± 0.6	2.6 ± 1	0.01
Pulmonary vascular arteriolar resistance, WU	22 ± 8	16 ± 12	0.04
Positive vasodilator response (n = 28, n = 220)	7	15	0.26

Values are % or mean ± SD. *p value obtained across groups.

6MW = 6-min walk; BNP = brain natriuretic peptide; DLCO = diffusion capacity of carbon monoxide; GFR = glomerular filtration rate; NYHA = New York Heart Association; PA = pulmonary arterial; PAH = pulmonary arterial hypertension; RA = right atrial; RV = right ventricular; WU = wood units.

of syncope. For the 84 patients who did not complete the questionnaire, clinical, echocardiographic, and right heart catheterization characteristics as well as mortality rates were similar to the 378 patients who formed the study group. There was no difference in the frequency of syncope reported with each survey revision (p = 0.88). Syncopal patients had a greater increase in heart rate (31 ± 12 beats/min vs. 25 ± 14 beats/min, p = 0.04) during their 6MW test and tended to have less increase in systolic blood pressure (9 ± 12 mm Hg vs. 13 ± 15 mm Hg, p = 0.12). The average fall in oxygen saturation with exercise was similar between groups. Few Holter monitors were obtained (n = 25) with no findings of significant dysrhythmia. Syncopal patients had higher RA pressures, lower cardiac outputs, and higher pulmonary vascular resistance indexes (Table 1).

Association of syncope with all-cause mortality. Overall 5-year mortality in the cohort was 52% with 174 events. Syncope was associated with a significantly increased risk of death (p = 0.01) (Fig. 1). In syncopal PAH patients, 1-, 3-, and 5-year survival rates were 69% (95% CI: 54% to 81%), 51% (95% CI: 36% to 65%), and 37% (24% to 53%), respectively, compared with 82% (95% CI: 77% to 86%), 64% (95% CI: 64% to 69%), and 54% (95% CI: 48% to 59%), respectively, in nonsyncopal patients. A probable cause of death could be ascertained in 106 (61%) patients (Fig. 2). In most patients PAH played a primary or secondary role in death; death was frequently preceded by a progressive decline in functional status and right heart failure. There was no apparent difference between syncopal and nonsyncopal patients as to the circumstances of death.

Patients with syncope, regardless of FC of dyspnea/fatigue, had a higher mortality rate than nonsyncopal FC 3 patients (p = 0.02) and a mortality rate similar to nonsyncopal FC 4 patients (p = 0.18) (Fig. 3).

Predictors of overall mortality. Univariate and multivariate factors associated with all-cause mortality are shown in Table 2. Established clinical, echocardiographic, and invasive predictors of poor prognosis predicted all-cause death in this cohort. Syncope carried an unadjusted HR of 1.75 (95% CI: 1.10 to 2.66) and an HR of 1.87 (95% CI: 1.17 to 2.86) when adjusted for age and sex. Less specific symptoms of dizziness and lightheadedness were not associated with mortality (data not shown). Stepwise incremental multivariate modeling demonstrated that syncope (HR: 1.94 [95%

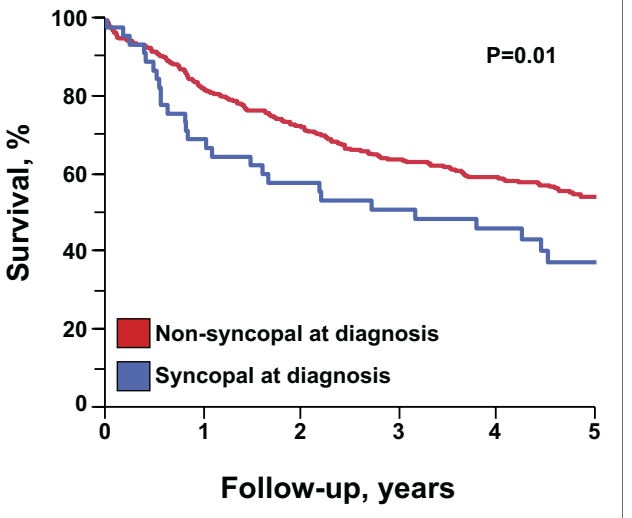

Figure 1 Kaplan-Meier Survival Estimates of Observed 5-Year Survival in PAH Patients Stratified by History of Syncope at Presentation

Syncope was significantly associated with an increased risk of death (p = 0.01). PAH = pulmonary arterial hypertension.

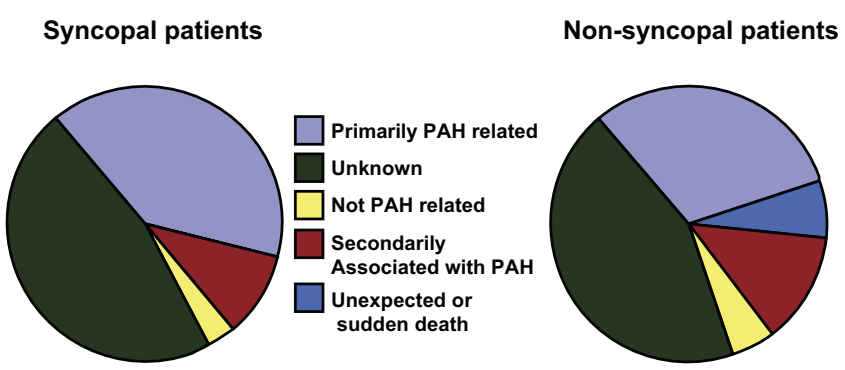

Figure 2 Available Data on Cause of Death in Syncopal and Nonsyncopal PAH Patients

There were no significant differences between groups. PAH = pulmonary arterial hypertension.

CI: 1.20 to 2.99]), remained a significant predictor of mortality even after adjusting for other listed factors (Table 2).

Discussion

The present study clarifies the incidence of syncope in patients with newly diagnosed PAH in the current era and describes the clinical and hemodynamic characteristics and the prognostic significance of syncope. To date, the implications of syncope in an adult with PAH have remained largely determined by expert opinion and case reports, and there is no consensus on how to interpret this symptom in PAH. We demonstrate that 12% of newly diagnosed PAH patients have a recent history of syncope. Syncope is associated with impaired right heart function but correlates poorly with functional status. Syncope is linked to an increased risk of death that is incremental to the risk attributable to other recognized prognostic factors.

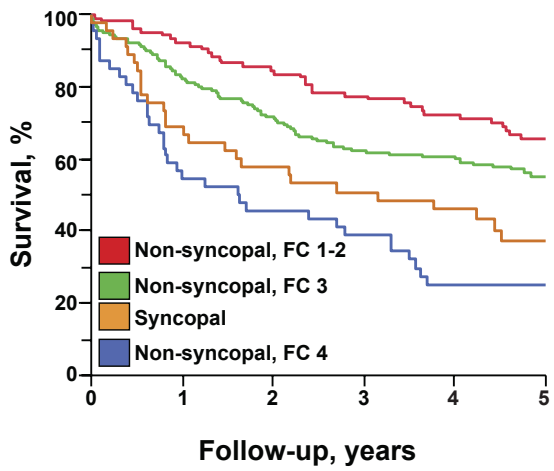

Figure 3 Kaplan-Meier Survival Estimates of Observed 5-Year Survival in PAH Patients Without Syncope Stratified by Their Dyspnea/Fatigue (FC) at Presentation and Syncopal Patients

Syncope is associated with a higher mortality than functional class (FC) 3 patients ($p = 0.02$) and is equivalent to FC 4 ($p = 0.18$). PAH = pulmonary arterial hypertension.

The mechanism of syncope in PAH remains ill-defined although likely is predominantly hemodynamic rather than arrhythmic (1,12–14), as seen in conditions of left ventricular pressure overload (15,16). Although the mechanism of syncope could not be established here, the cause of death in syncopal patients seemed similar to that of those without syncope. In both groups, few patients died unexpectedly, as might be expected if the primary mechanism of syncope was arrhythmic.

Although the methodology of this study has strengths, it also has potential limitations. The symptom questionnaire for classification of syncope allowed for a standardized assessment of the incidence of syncope, although the frequency, situation(s), severity, and timing of syncopal events was not recorded. The data do not allow us to comment on whether the syncope of each patient was mechanistically related to PAH. Development of syncope later in the course of the disease was not assessed. The cause of death was not reported in a standardized format and could not be ascertained in all patients. Comprehensive data on therapy after diagnosis was also not available. We focused this study on adults with PAH and are unable to comment on the prevalence and significance of syncope in the pediatric population where it might be different (17) or in the setting of other groups of PH. Finally, we are unable to comment on whether pre-syncope is also associated with mortality. Pre-syncope describes a clinical scenario that bridges the spectrum from lightheadedness (here unrelated to outcome) and syncope (here strongly associated with outcome). The study questions of lightheadedness and dizziness might not have adequately captured the presence of pre-syncope.

To our knowledge, this is the first study to show that syncope is an ominous sign in adults with PAH. We provide data establishing that syncope in PAH is associated with impaired right heart function. Even after adjusting for

Table 2 Univariate and Multivariate Predictors of All-Cause Mortality

	Unadjusted	Age- and Sex-Adjusted	Stepwise Inclusion/Exclusion Model
Clinical findings			
Age at diagnosis (per 10-yr)	1.28 (1.14–1.44); 0.001	1.31 (1.17–1.48); 0.001	1.12 (0.97–1.29); 0.1
Female (vs. male)	0.81 (0.59–1.14); 0.22	0.66 (0.47–0.94); 0.02	0.64 (0.44–0.95); 0.03
Syncope at presentation	1.75 (1.10–2.66); 0.01	1.87 (1.17–2.86); 0.01	1.94 (1.20–2.99); 0.008
Functional class	1.76 (1.37–2.26); 0.001	1.75 (1.36–2.25); 0.001	1.30 (0.98–1.74); 0.07
cPAH (vs. IPAH, other)	1.58 (1.21–2.03); 0.001	1.59 (1.21–2.06); 0.001	—
Noninvasive findings			
6MW (per 50-m decline)	1.34 (1.24–1.44); 0.001	1.33 (1.22–1.46); 0.001	1.22 (1.12–1.37); 0.001
GFR (per 10 cc/min/1.72 m^2 decline)	1.17 (1.06–1.28); 0.002	1.14 (1.03–1.27); 0.02	—
DLCO (per 10% decline)	1.40 (1.27–1.55); 0.001	1.37 (1.24–1.53); 0.001	1.10 (0.98–1.29); 0.1
Severe right ventricular enlargement	1.46 (1.08–1.97); 0.001	1.83 (1.33–2.51); 0.001	—
Estimated RA pressure (per 5 mm Hg)	1.76 (1.48–2.10); 0.001	1.80 (1.49–2.18); 0.001	1.57 (1.31–1.89); 0.001
Invasive findings			
Mean PA pressure (per 10 mm Hg)	1.03 (0.91–1.15); 0.67	1.14 (1.0–1.28); 0.04	—
Cardiac index (per 1 l/min/m^2)	0.65 (0.52–0.82); 0.001	0.65 (0.51–0.82); 0.001	—
RA pressure (per 5 mm Hg)	1.36 (1.18–1.55); 0.01	1.46 (1.25–1.67); 0.001	—

Values are HR (95% CI); p value.

CI = confidence interval; cPAH = pulmonary arterial hypertension in the setting of connective tissue disease; HR = hazard ratio; IPAH = idiopathic pulmonary arterial hypertension; PVRI = pulmonary vascular resistance index; other abbreviations as in Table 1.

traditional prognostic factors, syncope remained independently and strongly predictive of a poor prognosis, with a risk similar to that of FC 4 status. Future studies should aim to elucidate the mechanism of syncope in PAH and to determine the impact of treatment on the frequency and significance of syncope throughout the course of the disease.

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