Pulmonary Circulation

WILEY

PVRi | Pulmonary Circulation Open Access

RESEARCH LETTER OPEN ACCESS

Alterations in ECG and Right Heart Catheterization Data in PAH Patients Who Died From Sudden Death Compared With Right Heart Failure

Alexandra B. Flemington[1] | Jeffery Annis[2,3,4] | Evan L. Brittain[2,3,4] | Anna R. Hemnes[5]

[1]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA | [2]Department of Cardiology, Vanderbilt Institute for Clinical and Translational Research, Nashville, Tennessee, USA | [3]Vanderbilt Institute for Clinical and Translational Research, Nashville, Tennessee, USA | [4]Division of Cardiovascular Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA | [5]Division of Allergy, Pulmonary and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Correspondence: Anna R. Hemnes (Anna.r.hemnes@vumc.org)

Received: 5 February 2025 | **Revised:** 1 April 2025 | **Accepted:** 7 April 2025

Funding: This study was supported by K24 HL155891.

ABSTRACT

A meaningful number of patients with PAH die suddenly, and there is little data to understand the events surrounding sudden death in PAH. We tested the hypothesis that sudden death is associated with pre-mortem ECG or hemodynamics changes compared to those who died of RHF. We extracted data from the Vanderbilt University Medical Center Synthetic Derivative. Patients 18 years of age and older with Group 1 PAH secondary to any etiology who died between 2009 and 2017 with both ECG and RHC data from the inpatient and outpatient setting were included in the study. Continuous variables were compared using the Wilcoxon rank-sum test while categorical variables were compared using the χ^2 test. Logistic regression models, adjusted for age and sex, were then used to evaluate the association between death and specific ECG or RHC measurements. Comparing the final ECG before death, those who died of SD had significantly shorter terminal 40 ms interval of the QRS than those who died of RHF, which became nonsignificant when adjusted for age and sex. We observed differences in baseline RHC data between SD and RHF including higher RV systolic pressure which remained significant when adjusted for age and sex. Using this data, we hope to find clinical data that can be used to predict increased risk of sudden death and aid in stratifying Group I PAH patients to earlier and more aggressive interventions.

1 | Introduction

Pulmonary arterial hypertension (PAH) is a rare disease state in which normally low-pressure pulmonary vasculature develops higher resistances and pressures. Even with current treatment, mortality remains high, with recent publications reporting nearly a third of patients died 32 months after diagnosis [1]. Although the most common cause of death in PAH is right heart failure (RHF), about half of patients with PAH die suddenly [2, 3].

The underlying cause of sudden death in PAH is unknown but is postulated to involve fatal arrhythmias secondary to right heart failure. Currently, there is no framework for identifying patients at high risk for sudden death (SD). Prior work has used ECG and right heart catheterization (RHC) data to create general risk scores for all-cause mortality to guide treatment with some parameters associated with higher all-cause mortality [4–10]; however, there are no risk scores specifically for SD in PAH patients. If PAH patients at risk for SD could be identified, monitoring to specifically identify an arrhythmia as an

Evan L. Brittain and Anna R. Hemnes are co-last authors.

underlying cause of SD or trials of intervention could be pursued when this risk is identified.

To better identify PAH patients at elevated risk for SD, we tested the hypothesis that sudden death is associated with premortem ECG or hemodynamics changes compared to those who died of RHF. We used a deidentified medical record to study longitudinal changes in ECG and invasive hemodynamic measurements in subjects with PAH who died, comparing findings in subjects with SD with those from patients who died of RHF.

2 | Methods

We extracted data from the Vanderbilt University Medical Center Synthetic Derivative, a deidentified version of the Vanderbilt electronic medical health record originating in 1995. The design and implementation of the synthetic derivative have been previously described [11, 12]. We included patients aged 18 and older who met contemporary consensus criteria for group 1 PAH confirmed by expert clinicians with mPAP of >25 mmHg and a PVR of >3 Woods Units. Patients with PAH secondary to any etiology who died between 2009 and 2017 with both ECG and RHC data from the inpatient and outpatient setting were included. Patients with PAH who received a heart or lung transplant or who were enrolled in hospice were excluded from this study. Baseline characteristics extracted included age, sex, BMI, race, etiology of PAH, 6-min walk test distance (6MWD), functional class, and Borg dyspnea index. We obtained quantitative measures reported in the first ECG and ECG closest to death. ECG measures included PR interval, QTc interval, QRS duration, P-wave, and heart rate. Quantitative pressure measurements were obtained from the first RHC and RHC closest to death, which included mean pulmonary arterial pressure (mPAP), cardiac index (CI), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR), and right ventricular systolic pressure (RVSP). The cause of death was ascertained from a manual chart review by expert clinicians. Patients who died due to arrhythmia, pulseless electrical activity, or died suddenly at home were included in the "sudden death" group, and those whose cause of death were RHF/cardiogenic shock were included in the "RHF" group, which also included patients diagnosed with RHF who experienced a sudden event that led to death.

Continuous variables were compared between the sudden death group and the RHF group using the Wilcoxon rank-sum test. Categorical variables were compared using the chi-square test. Logistic regression models, adjusted for age and sex, were employed to evaluate the association between death and specific ECG or RHC measurements. A Kaplan–Meier analysis was conducted to assess the time-to-death outcomes between the groups.

3 | Results

In total, there were 117 patients within the synthetic derivative, of which 85 had group I PAH with 31 of these patients meeting our full inclusion criteria (90% female, 52 years [44.8–63.8]) including 16 patients who died suddenly and 15 who died from RHF/cardiogenic shock. The other 32 patients that were excluded had causes of death attributed to other events, such as sepsis, did not have group 1 PAH, or were lung/heart transplant recipients. Demographics between the groups were similar (Figure 1A). Metrics of disease severity commonly used were similar between the groups, including functional class and 6MWD, though BNP was lower in the SD group.

When comparing the first recorded ECG, patients who died of SD had no differences in ECG compared to those who died of RHF. This included QTc interval, mean QRS duration, and PR interval. Comparing the final ECG before death, those who died of SD had significantly shorter terminal 40 ms interval of the QRS than those who died of RHF (139.2 ± 25.4 vs. 162.7 ± 32.6, $p = 0.02$) (Figure 1B) which was no longer significant when adjusted for age and sex ($p = 0.06$). Other measures were not different between groups, including QTc interval, mean QRS duration, and PR interval. The duration between the first ECG performed and the date of death, as well as the last ECG, performed and the date of death, also did not differ between groups.

We observed differences in baseline RHC data between SD and RHF, including higher RV systolic pressure (97.9 ± 17.2 vs 78.8 ± 16.5, $p = 0.03$; Figure 1C), which remained significant when adjusted for age and sex ($p = 0.04$). There were several measurements that were not different between groups, including mean arterial blood pressure, systolic blood pressure, mean pulmonary artery pressure, PCWP, PVR, and cardiac index by Fick (CiF). When comparing the last RHC data before death, there were no significant differences between these measurements. The duration between the first RHC and date of death and the last RHC and date of death was also not significantly different between the groups.

In a Kaplan–Meier analysis, the time to death was similar between the group with SD vs those with RHF ($p = 0.97$, Figure 1D).

4 | Conclusions

We used a comprehensive deidentified medical record to compare PAH patients who died of SD compared to RHF. Importantly, about half of the included subjects died of SD, and this occurred in a similar timeline to subjects who died of RHF, suggesting a key role for this poorly understood phenomenon of PAH. Clinical differences between patients who died of SD versus RHF were subtle, and there were no defining demographic differences with the exception of a lower BNP in the SD group. Further, baseline ECG was not different between the groups, while patients with PAH who died of SD did have significantly shorter terminal 40 ms of the QRS in their final ECG before death. This is clinically important as the terminal portion of the QRS can be indicative of changes in conduction through the ventricles, and these changes have been associated with an increased risk of ventricular arrhythmias and worse clinical outcomes [13, 14]. Interestingly, patient who died of SD had higher RVSP on index RHC, including after adjustment for age

A: Baseline Characteristics

	Sudden Death N=16	Right Heart Failure N=15	P-value
Age at diagnosis (years)	51.1±14.9	53.0±13.2	0.71
Mean Age at death (years)	53.3±15.8	56.4±12.2	0.44
Female sex (%)	15/16 (94)	13/15 (87)	0.37
White race (%)	15/16 (94)	14/15 (93)	0.51
Median BMI	39.9±14.8	33.3±10.3	0.25
Mean RAP	11.3±5.6	9.1±5.7	0.57
mPAP	62.1±11.9	52.1±10.6	0.09
Mean PCWP	12.0±6.0	8.8±4.2	0.24
BNP prior to death with date	813±928	1974±2322	0.03*
CI (Fick)	3.49±2.98	2.55±0.70	0.86
PVR	20.2±20.0	12.1±5.44	0.44
Functional Class (%)			0.59
1	0/15 (0)	0/15 (0)	
2	3/15 (20)	3/15 (20)	
3	11/15 (73)	12/15 (80)	
4	1/15 (7)	0/15 (0)	
6-Minute Walk Distance (meters)	297±1.52	277±132	0.86
Dyspnea Index	2.81±1.52	2.86±1.96	0.42
Type of PAH (%)			0.37
Idiopathic	9/16	6/15	
Scleroderma	3/16	5/15	
Portopulmonary	1/16	2/15	
CTD	2/16	1/15	
RA	1/16	0/15	
Other	0/16	1/15	
Age at first ECG	48.6±15.5	52.0±13.1	0.42
Age at first RHC	51.1±14.9	53.0±13.2	0.71

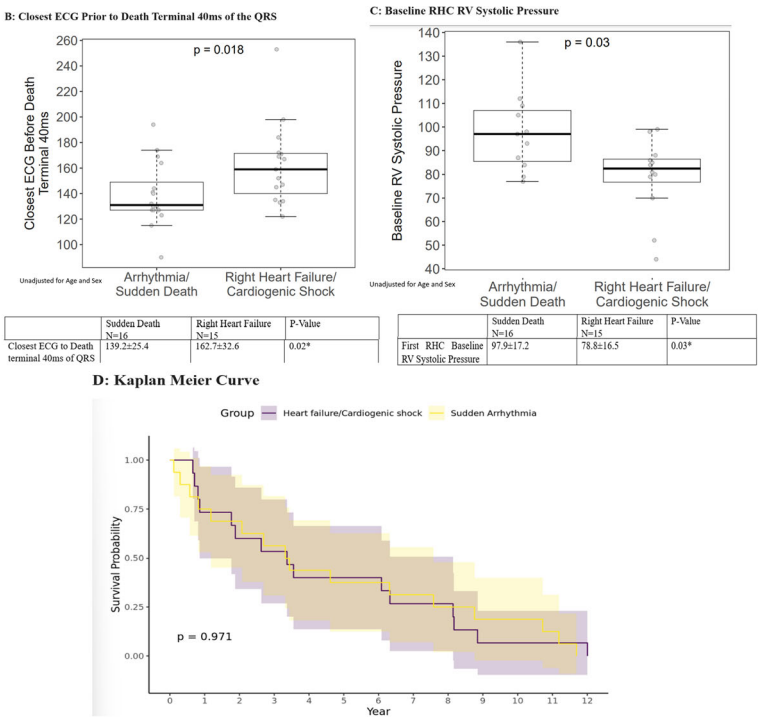

FIGURE 1 | (A) Baseline characteristics of included subjects. (B) Closest ECG before death terminal 40 ms of the QRS. (C) Baseline RHC RV Systolic Pressure. (D) Kaplan–Meier Curve in sudden death compared with right heart failure. CI, cardiac index; CTD, connective tissue disease; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterization.

and sex, but did not have more alteration in CI or PVR. Overall, these data suggest that subjects with SD may have had more compensated PAH, but did not have evidence of more severe disease than their counterparts with RHF.

Our study supports prior work demonstrating the common occurrence of SD in PAH [4–10]. These patients also die in a similar timeline during their disease compared to patients who die of RHF demonstrated by the Kaplan–Meier analysis. The study also suggests that there are recognizable differences in ECG measurements over time and in initial RHC hemodynamics that undergo dynamic changes that could predict an increased risk of sudden death early in the PAH course. Based on our results, risk of SD may be able to be predicted early on in a patient's PAH disease in patients with compensated hemodynamics at the time of diagnosis. There do not seem to be significant differences in initial ECG measurements between these patients that could be used to risk stratify patients at risk for SD, though differences may arise over the course of their disease that could be a marker used for monitoring.

These findings suggest that patients who died by SD may be identified by ECG measurements over the course of their disease, specifically the terminal 40 ms of the QRS. This was a novel finding, as this portion of the ECG has traditionally been utilized to monitor for TCA toxicity or inferior myocardial infarctions [15, 16]. These patients' right-sided pressures were more compensated as seen in the higher RV systolic pressure at the time of diagnosis, suggesting that these patients had more preserved RV function. This difference disappeared as time progressed, suggesting progressive decompensation as the ability to maintain RV systolic pressure declined, which describes the natural course of PAH.

Further study is warranted to understand ECG and RHC predictors of sudden death in PAH. With improved knowledge in this area, providers may be able to better risk stratify patients into risk groups for SD, allowing for the advancement of therapies sooner and more aggressively for patients at higher risk for SD from PAH.

Author Contributions

Hypothesis generation and project development: Alexandra B. Flemington, Evan L. Brittain, Anna R. Hemnes. Data analysis: Alexandra B. Flemington and Jeffery Annis. Data generation: Alexandra B. Flemington. Statistical analysis: Jeffery Annis. Manuscript drafting and editing: Alexandra B. Flemington, Jeffery Annis, Evan L. Brittain, Anna R. Hemnes.

Acknowledgments

The authors have nothing to report.

Ethics Statement

The local Institutional Review Board approved the study.

Conflicts of Interest

Anna R. Hemnes: Consulting: GossamerBio, Merck, United Therapeutics, Bayer, Tenax Therapeutics. Stockholder: Tenax Therapeutics. The other authors declare no conflicts of interest.

Alexandra B. Flemington
Jeffery Annis
Evan L. Brittain
Anna R. Hemnes

References

1. A. Boucly, L. Savale, X. Jaïs, et al., "Association Between Initial Treatment Strategy and Long-Term Survival in Pulmonary Arterial Hypertension," *American Journal of Respiratory and Critical Care Medicine* 204, no. 7 (October 2021): 842–854.

2. A. R. Tonelli, V. Arelli, O. A. Minai, et al., "Causes and Circumstances of Death in Pulmonary Arterial Hypertension," *American Journal of Respiratory and Critical Care Medicine* 188, no. 3 (August 2013): 365–369.

3. M. Delcroix and R. Naeije, "Optimising the Management of Pulmonary Arterial Hypertension Patients: Emergency Treatments," *European Respiratory Review* 19, no. 117 (September 2010): 204–211.

4. M. Waligóra, A. Tyrka, P. Podolec, et al., "Corrigendum to "ECG Markers of Hemodynamic Improvement in Patients With Pulmonary Hypertension"," *BioMed Research International* 2018 (August 2018): 1.

5. A. Vraka, E. Diamanti, M. Kularatne, et al., "Risk Stratification in Pulmonary Arterial Hypertension, Update and Perspectives," *Journal of Clinical Medicine* 12, no. 13 (June 2023): 4349.

6. P. M. Hendriks, R. M. Kauling, L. W. Geenen, et al., "Role of the Electrocardiogram in the Risk Stratification of Pulmonary Hypertension," *Heart* 109, no. 3 (September 2022): 208–215.

7. T. A. Michalski, J. Pszczola, A. Lisowska, et al., "ECG in the Clinical and Prognostic Evaluation of Patients With Pulmonary Arterial Hypertension: An Underestimated Value," *Therapeutic Advances in Respiratory Disease* 16 (January 2022): 17534666221087846, https://doi.org/10.1177/17534666221087846.

8. L. Ley, R. Höltgen, H. Bogossian, H. A. Ghofrani, and D. Bandorski, "Electrocardiogram in Patients With Pulmonary Hypertension," *Journal of Electrocardiology* 79 (July 2023): 24–29, https://www.sciencedirect.com/science/article/abs/pii/S002207362300033X.

9. M. Waligóra, A. Tyrka, P. Podolec, and G. Kopeć, "ECG Markers of Hemodynamic Improvement in Patients With Pulmonary Hypertension," *BioMed Research International* 2018 (2018): 1–10.

10. K. Barańska-Pawełczak, C. Wojciechowska, and W. Jacheć, "Diagnostic and Predictive Value of Right Heart Catheterization-Derived Measurements in Pulmonary Hypertension," *Wiadomości lekarskie* 74, no. 3 cz 1 (January 2021): 546–553.

11. D. M. Roden, J. M. Pulley, M. A. Basford, et al., "Development of a Large-Scale De-Identified DNA Biobank to Enable Personalized Medicine," *Clinical Pharmacology and Therapeutics* 84, no. 3 (May 2008): 362–369.

12. J. Pulley, E. Clayton, G. R. Bernard, D. M. Roden, and D. R. Masys, "Principles of Human Subjects Protections Applied in an Opt-Out, De-Identified Biobank," *Clinical and Translational Science* 3, no. 1 (February 2010): 42–48.

13. A. Takagi, K. Nakazawa, T. Sakurai, T. Nanke, and F. Miyake, "Prolongation of LAS40 (Duration of the Low Amplitude Electric Potential Component (<40.MU.V) of the Terminal Portion of the QRS) Induced by Isoproterenol in 11 Patients With Brugada Syndrome," *Circulation Journal* 66, no. 12 (2002): 1101–1104.

14. C. W. Lee, M. K. Hong, H. S. Yang, et al., "Determinants and Prognostic Implications of Terminal QRS Complex Distortion in Patients Treated With Primary Angioplasty for Acute Myocardial Infarction," *American Journal of Cardiology* 88, no. 3 (August 2001): 210–213.

15. T. R. Wolfe, E. Martin Caravati, and D. E. Rollins, "Terminal 40-ms Frontal Plane QRS Axis as a Marker for Tricyclic Antidepressant Overdose," *Annals of Emergency Medicine* 18, no. 4 (April 1989): 348–351.

16. R. A. Warner, J. Battaglia, N. E. Hill, S. Mookherjee, and H. Smulyan, "Importance of the Terminal Portion of the QRS in the Electrocardiographic Diagnosis of Inferior Myocardial Infarction," *American Journal of Cardiology* 55, no. 8 (April 1985): 896–899.