Title

Echocardiographic assessment of pulmonary arterial capacitance predicts mortality in pulmonary hypertension

Journal

Journal of Cardiology, 77(3)

ISSN

0914-5087

Authors

Papolos, Alexander
Tison, Geoffrey H
Mayfield, Jacob
et al.

Publication Date

2021-03-01

DOI

10.1016/j.jjcc.2020.10.006

Peer reviewed

HHS Public Access

Author manuscript

J Cardiol. Author manuscript; available in PMC 2022 March 01.

Published in final edited form as:

J Cardiol. 2021 March ; 77(3): 279–284. doi:10.1016/j.jjcc.2020.10.006.

Echocardiographic Assessment of Pulmonary Arterial Capacitance Predicts Mortality in Pulmonary Hypertension

Alexander Papolos, MD[a,*], **Geoffrey H Tison, MD, MPH**[b,c,d,e,*,†], **Jacob Mayfield, MD**[c], **Elena Vasti, BS**[f], **Teresa DeMarco, MD**[b,c]

[a]Department of Cardiology, MedStar Washington Hospital Center, Washington, DC, USA

[b]Division of Cardiology, University of California, San Francisco, CA, USA

[c]Department of Medicine, University of California, San Francisco, CA, USA

[d]Bakar Computational Health Sciences Institute, University of California, San Francisco, CA, USA

[e]Cardiovascular Research Institute, University of California, San Francisco, CA, USA

[f]Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA

Abstract

Background: Pulmonary arterial capacitance (PAC) is one of the strongest predictors of clinical outcomes in patients with pulmonary hypertension (PH). We examined the value of an echocardiographic surrogate for PAC (ePAC) as a predictor of mortality in patients with PH.

Methods: We performed a retrospective study of 302 patients with PH managed at a PH comprehensive care center over a cumulative follow-up time of 858 patient-years. Charts from 2004 to 2018 were reviewed to identify patients in whom a right heart catheterization (RHC) was performed within two months of an echocardiogram. Standard invasive, non-invasive, functional, and biochemical prognostic markers were extracted from the time of RHC. The primary outcome was all-cause mortality. Cox proportional hazards models were used to model the time from RHC to the primary outcome or last medical contact.

Results: Variables associated with all-cause mortality included ePAC [standardized hazard ratio (HR) 0.68, 95% CI 0.48-0.98, p=0.036], RHC-PAC (HR 0.68, 95% CI 0.48-0.96, p=0.027), echocardiographic pulmonary vascular resistance (HR 1.29, 95% CI 1.05-1.60, p=0.017), six-minute walk distance (HR 0.43, 95% CI 0.23-0.82, p=0.01), and B-type natriuretic peptide (HR 1.29, 95% CI 1.03-1.62, p=0.027). In multivariable-adjusted Cox analysis, ePAC predicted all-cause mortality independently of age, gender, and multiple comorbidities. There was a graded

[†]Corresponding Author: Geoffrey H Tison, MD MPH, 555 Mission Bay Blvd South Box 3120, San Francisco, CA 94158, USA, Tel: +1-415-514-0992; Fax: +1-415-502-7949, Geoff.tison@ucsf.edu.

[*]Alexander Papolos and Geoffrey H Tison contributed equally as co-first authors.

Author contributions: AP and GHT had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. AP, GHT, TD, JM, and EV contributed substantially to the study design, data analysis, and interpretation, and the writing of the manuscript.

and stepwise association between low (<0.15 cm/mmHg), medium (0.15-0.25 cm/mmHg), and high (>0.25 cm/mmHg) tertiles of ePAC and all-cause mortality.

Conclusions: We have demonstrated that ePAC is a readily available echocardiographic marker that independently predicts mortality in PH, and have provided clinically relevant ranges by which to risk-stratify patients and predict mortality.

Keywords

Pulmonary hypertension; Pulmonary arterial capacitance; Right ventricular-pulmonary arterial coupling; Echocardiography; Survival

Introduction

Pulmonary hypertension (PH) affects 1% of the global population, an estimated 50-70 million people, and is associated with increased mortality, reduced quality of life, and significant healthcare costs [(1, 2)]. PH is an umbrella term that encompasses a complex spectrum of diseases, each of which places strain on the right ventricle, and can ultimately lead to right ventricular dysfunction and failure. The right ventricle is a thin-walled chamber which functions to pump blood through a low pressure, high capacitance vascular bed. While its structure allows it to tolerate large shifts in volume, the right ventricle is ill-equipped to overcome significant increases in afterload [(3–6)]. The pulmonary arteries and arterioles are considerably elastic, which is a mechanically favorable adaptation that mitigates afterload elevation during systole and dampens pulse-wave reflection to minimize right ventricular work [(7)]. Pulmonary arterial capacitance (PAC) is a quantitative measure of pulmonary arterial elasticity that is easily calculated from right heart catheterization (RHC) and is defined as the right ventricular stroke volume divided by the pulmonary arterial pulse pressure. Several studies have shown that PAC is a superior predictor of mortality in patients with PH when compared to conventional invasive metrics, including pulmonary vascular resistance (PVR), cardiac index, and mean pulmonary arterial pressure [(8–13)].

While hemodynamic measurements obtained by RHC are important for defining both PH etiology and severity, RHC is an invasive procedure that is associated with tangible risks to the patient while also being time and resource intensive. Due to these limitations, echocardiography is commonly used for routine, long-term PH monitoring. Our group has previously demonstrated that a ratio of the right ventricular outflow tract velocity time integral ($RVOT_{VTI}$) to the peak arterial systolic pressure (ePASP) obtained by transthoracic echocardiography can be used as a non-invasive surrogate for PAC, which we refer to as ePAC [(14)]. The aim of this study was to determine the prognostic value of the ePAC compared to standard invasive, non-invasive, functional, and biochemical markers in patients with PH.

Methods

Study design and patients.

We conducted a retrospective study of adult patients with PH diagnosed and managed at a PH comprehensive care center from a tertiary care hospital. Manual chart review of consecutive electronic medical records was performed on patients with at least one clinic encounter from 2004 to 2018. Patients were eligible for inclusion if they had undergone RHC within two months of a transthoracic echocardiogram that reported ePASP and $RVOT_{VTI}$ measurements for the calculation of ePAC. Out of a total of 696 patients screened, 368 were identified to have undergone both RHC and transthoracic echocardiogram, and of these, 302 had both the $RVOT_{VTI}$ and ePASP reported (Fig. 1). Baseline information of the 302 patients was collected from the time of RHC, including age, gender, race, ethnicity, cardiovascular comorbidities, World Health Organization (WHO) PH group and functional class, pulmonary vasodilator use, six-minute walk distance, smoking history, and B-type natriuretic peptide.

The primary outcome was defined as all-cause mortality, which was adjudicated through manual review of the electronic medical record. Time at risk was calculated from the time of the RHC used to establish study inclusion to the first occurrence of either clinical outcome or last medical contact. The University of California San Francisco (UCSF) Institutional Review Board approved this study (IRB number 13-11983) and approved a waiver of informed consent.

Right heart catheterization.

Cardiac catheterizations were performed as part of routine clinical care and standard catheterization laboratory protocol was used for RHC. PVR, indirect Fick cardiac output/index, right atrial pressure, pulmonary arterial systolic/diastolic/mean pressure, and pulmonary capillary wedge pressure were extracted from procedure reports. Stroke volume was calculated by dividing the indirect Fick cardiac output by the heart rate. PAC was determined by dividing stroke volume by the pulmonary arterial pulse pressure. Pulmonary arterial pulsatility index was defined as the pulmonary arterial pulse pressure divided by the right atrial pressure. We performed a sensitivity analysis in those who had available cardiac output measurements estimated by thermodilution and did not find materially different results. Therefore, since indirect Fick cardiac output data were available for 298 patients and thermodilution was available for only 241 patients, we chose to report results using only the indirect Fick equation for cardiac output.

Echocardiography.

Transthoracic echocardiography was performed and interpreted by the UCSF echocardiography laboratory (UCSF, San Francisco, CA, USA), and data were extracted from generated reports. Left ventricular ejection fraction was determined by Simpson's biplane method of disks. The $RVOT_{VTI}$ was measured using the subpulmonic valve pulse wave Doppler signal obtained from the parasternal short-axis view. The tricuspid annular plane systolic excursion (TAPSE) was measured using M-mode to determine the maximal systolic excursion of the lateral tricuspid annulus obtained in the apical four-chamber view.

The ePASP was calculated using the modified Bernoull equation: four times the peak tricuspid regurgitation jet velocity squared, plus the right atrial pressure determined by size and collapsibility of the inferior vena cava [(15)]. ePAC was defined as the $RVOT_{VTI}$ divided by the ePASP. Echocardiographic estimation of the PVR (ePVR) was determined via the modified Abbas formula: tricuspid regurgitation velocity squared divided by the $RVOT_{VTI}$ multiplied by five [(16)]. Right ventricular size was reported as normal, mild, moderate, or severe enlargement.

Statistical Analysis

Continuous variables are presented as means ± standard deviations (SD). Correlations between continuous variables are described using Pearson's correlation coefficients. Cox proportional hazards models were used to model the time from RHC to the primary outcome or last medical contact. Univariate Cox models were fitted to each predictor and the primary outcome. Multivariable-adjusted Cox models were fitted to ePAC to examine the independence of the association with all-cause mortality. Tertiles of ePAC were calculated based on our cohort distribution, and 10-year survival was explored. ePAC tertiles were then recalculated to correspond to prespecified cut-points (low <0.15, medium 0.15-0.25, and high >0.25) which approximated our population tertiles and are more easily clinically applied. Survivor functions are plotted to display 10-year survival, and we report 1-, 5-, and, 10-year survival in our cohort. Statistical analyses were performed using STATA 13 (College Station, TX, USA).

Results

Patients

Out of a total of 302 patients (Fig. 1), 68% were female and the mean age was 55 years (SD 14.5) (Table 1). The majority of patients had WHO group-1 PH (65%), followed by group-2 (15%), group-3 (9%), group-4 (6%), and group-5 (2%). The median WHO functional class was three. At enrollment 45% of patients were on a phosphodiesterase-5 inhibitor, 23% were on an endothelin receptor antagonist, and 15% were on a prostacyclin analog. Mean invasively measured PVR was 7.9 Wood units (SD 5.3), mean pulmonary arterial pressure was 42.9 mmHg (SD 13.6), and mean PAC was 1.9 mL/mmHg (SD 1.4). Mean non-invasively measured ePVR was 6.3 Wood units (SD 4.2), mean ePASP was 68.7 mmHg (SD 23.6), and mean ePAC was 0.3 cm/mmHg (SD 0.2).

Predictive value of ePAC

Over a cumulative follow-up of 846 patient-years and a median follow-up time of 8.6 years, there were a total of 63 deaths. Predictors associated with all-cause mortality included ePAC (standardized hazard ratio 0.68, 95% CI 0.48-0.98, p=0.036), PAC (standardized hazard ratio 0.68, 95% CI 0.48-0.96, p=0.027), ePVR (standardized hazard ratio 1.29, 95% CI 1.05-1.60, p=0.017), six-minute walk distance (standardized hazard ratio 0.43, 95% CI 0.23-0.82, p=0.01), and B-type natriuretic peptide (standardized hazard ratio 1.29, 95% CI 1.03-1.62, p=0.027) (Fig. 2). PVR, cardiac index, mean pulmonary arterial pressure, pulmonary arterial pulsatility index, TAPSE, ePASP, and right ventricular size were not associated with all-cause mortality.

We fit a multivariable-adjusted Cox model to examine whether ePAC was an independent predictor of all-cause mortality. ePAC remained an independent predictor of all-cause mortality (standardized hazard ratio 0.65, 95% CI 0.45-0.95, p=0.027) after adjustment for age, gender, and comorbidities including coronary artery disease, hypertension, diabetes, obesity, smoking history, and chronic obstructive pulmonary disease (Table 2).

When ePAC was divided into tertiles, there was a graded and stepwise association between ePAC tertile and all-cause mortality (Fig. 3). The cut-points for tertiles of ePAC were low <0.15 cm/mmHg (range 0.041-0.149), medium 0.15-0.25 cm/mmHg (range 0.151-0.247), and high >0.25 cm/mmHg (range 0.261-1.333). There was a significant survival difference by ePAC tertile (log-rank test for equality chi-Squared=12.9, p-value=0.002). The overall 1-, 5-, and 10-year survival rates according to ePAC tertiles in our cohort were low ePAC 88%, 61%, and 27%; medium ePAC 91%, 72%, and 41%; and high ePAC 96%, 86%, and 67%, respectively.

When we limited analysis to individuals with WHO group-1 PH (n=196), ePAC remained a significant predictor of all-cause mortality (standardized hazard ratio 0.47, 95% CI 0.27-0.83, p=0.009). Tertiles of ePAC continued to show a graded stepwise association with all-cause mortality (Fig. 4), and there remained a significant survival difference between ePAC tertiles (log-rank test for equality chi-Squared=11.28, p-value=0.004). In multivariable Cox analysis, ePAC remained predictive of all-cause mortality (standardized hazard ratio 0.41, 95% CI 0.22-0.77, p=0.005) after adjustment for age, gender, and comorbidities including coronary artery disease, hypertension, diabetes, obesity, smoking history, and chronic obstructive pulmonary disease. ePAC became borderline significantly associated with all-cause mortality, though with a strongly-consistent direction of association, after additionally adjusting for 6-minute walk distance (standardized hazard ratio 0.34, 95% CI 0.11-1.02, p=0.056).

Discussion

Pulmonary arterial capacitance has been identified as the strongest hemodynamic predictor of mortality in both PH and heart failure, leading to growing advocacy for its adoption into clinical practice [(6, 9, 17–19)]. In prior work, we demonstrated that ePAC is an echocardiographic surrogate for PAC across a spectrum of patients and hemodynamic profiles [(14)]. Here we further demonstrate its value as a marker of mortality in a real-world population of patients with WHO Group 1-5 PH. The performance of ePAC to predict mortality in our cohort was similar to that for invasive PAC, and remained significant after multivariable adjustment for age, gender, and comorbidities. ePAC also strongly predicted all-cause mortality amongst those with Group 1 PH. Importantly, we present clinically applicable ranges of ePAC that can be used for risk stratification and mortality prediction.

Conventional echocardiographic methods of describing right ventricular function including the ePASP, TAPSE, right ventricular fractional area of change, and right ventricular Doppler tissue imaging can be misleading in the setting of PH. While each of these metrics provides a quantitative measure of the right ventricle’s systolic function, none adequately accounts for the dynamic mechano-energetic relationship it shares with the vascular conduit to

which it is coupled. This limitation is exemplified by two common clinical dilemmas posed when interpreting the echocardiogram of a patient with PH. The first is how to appropriately describe the function of a right ventricle that quantitatively and qualitatively appears impaired, but nonetheless is producing near-systemic or supra-systemic pressures. This illustrates that ventricular function must be described within the context of its loading conditions. The second dilemma arises when there has been a reduction in the ePASP compared to a prior study. Assuming there has been no significant change in cardiac output, the reader is left to infer that there has been either a decrease in afterload or a decline in right ventricular systolic function. Therefore, the interpretation of decreased ePASP could suggest either treatment success or treatment failure and worsening PH. These scenarios highlight the need for echocardiographic metrics capable of evaluating the relationship between right ventricular function and the pulmonary circulation. ePAC is a numerically simple metric that describes the relationship between right ventricular stroke volume ($RVOT_{VTI}$) and the peak pulmonary pressure generated (ePASP), which is a function of the pulmonary vasculature's impedance to accommodate the ejected blood volume. By using this ratio of stroke volume to the associated pressure generated, the ePAC measurement controls for changes in both cardiac output and vascular impedance, thus preserving its validity under various loading conditions.

In this study, we take the additional step to demonstrate that tertiles of ePAC predict incident clinical outcomes in a graded stepwise fashion, allowing for stratification into low-, medium-, and high-risk groups. In the absence of PH, the $RVOT_{VTI}$ should be more than half the ePASP, and thus the ePAC should be >0.5 cm/mmHg, signifying maintenance of right ventricular-pulmonary arterial coupling. In PH, however, reduction of ePAC quantitatively describes the degree to which increased afterload is causing right ventricular dysfunction and uncoupling between the right ventricle and pulmonary circulation. Therefore, a low ePAC identifies patients at increased risk of right ventricular failure. Based on data from our cohort, an ePAC greater than 0.25 cm/mmHg in a PH patient is associated with a projected 5-year mortality of 14% (low-risk), which increases to 28% when the ePAC is 0.15-0.25 cm/mmHg (medium-risk), and further to 39% when the ePAC falls below 0.15 cm/mmHg (high-risk).

Invasively, the PAC can be calculated from a standard RHC by dividing the cardiac stroke volume by the pulmonary arterial pulse pressure (systolic – diastolic pressure). An analogous echocardiographic method for calculating PAC was described by Mahapatra et al. in 2006 [(20)]. This method utilized the $RVOT_{VTI}$ as a surrogate for stroke volume, the peak tricuspid regurgitant gradient plus the estimated right atrial pressure for pulmonary systolic pressure, and the end-diastolic pulmonic regurgitation jet velocity plus the estimated right atrial pressure for the pulmonary arterial diastolic pressure [$RVOT_{VTI}$ (ePASP – pulmonary arterial diastolic pressure)]. In a sample of 54 patients with pulmonary arterial hypertension the authors reported that their method for calculating ePAC was the only non-invasive predictor of mortality. While this method may more accurately reflect the definition of PAC, the authors found that only 52% of the patients screened for enrollment had a sufficient pulmonary regurgitation signal required to determine pulmonary arterial diastolic pressure. By removing the pulmonary arterial diastolic term from the equation as we have done in the current study, we have increased the ability to calculate ePAC to 82%

of echocardiograms since ePASP is more widely available. Furthermore, since our data were obtained retrospectively from studies that were not intended for the calculation of ePAC, we suspect that an even higher yield is possible if echocardiograms are attempted prospectively for this metric.

Calculation of ePAC is similar to the widely accepted modified Abbas formula for calculating ePVR in patients with PH [(16)]. This likeness is a reflection of the inverse hyperbolic relationship that exists between PVR and PAC [(21)]. This relationship predicts that PAC is a more sensitive marker of early pulmonary vascular disease than is PVR, which may explain its superior prognostic ability [(22)]. The formulaic similarity between ePAC and ePVR explains their similar (inverse) performance in predicting all-cause mortality. The primary distinction between the two formulae is that ePAC utilizes the modified Bernoulli equation and accounts for right atrial pressure to derive an estimated pressure (ePASP) rather than relying on the tricuspid regurgitation velocity alone.

In addition to ePAC, we found that PAC, ePVR, six-minute walk distance, and B-type natriuretic peptide were also associated with mortality, which is consistent with prior studies [(11, 13, 23–25)]. We suspect that our failure to validate other previously described predictors of mortality including cardiac index, PVR, PASP, TAPSE, and right ventricular size is a reflection of the strength of association of each variable and the modest sample size of our population [(11, 13, 25)].

Limitations

This study has several limitations, most notably its retrospective single-center study design. Additionally, the sample was restricted to patients in whom RHC and transthoracic echocardiogram were temporally related within a 2-month period. A smaller temporal window would have allowed for more biologically accurate comparisons between invasive and non-invasive parameters at the cost of sample size. In terms of the quantitative non-invasive metrics of right ventricular function assessed in this study, we were limited to those reported per the conventions of our institution.

Conclusion

We have demonstrated that ePAC is a readily available echocardiographic marker that independently predicts mortality in PH, and have provided clinically relevant ranges by which to risk-stratify patients and predict mortality.

Acknowledgments

Funding information: Dr Tison received support from the National Institutes of Health (K23 HL135274). The funding source was not involved in study design, analysis, or decision to submit the article for publication.

Financial/nonfinancial disclosures: Dr Tison received support from the National Institutes of Health (K23 HL135274) and has received research grants from Janssen Pharmaceuticals Inc. Dr DeMarco: Johnson & Johnson/ Actelion: Consultant, speaker, advisory boards, steering committee member for a global study, DSMB member for US trial; United Therapeutics: Adjudication committee member; Acceleron: Research funding for multi center trial; SCOPE/Bial: Data, safety, and monitoring board member.

Declaration of interests: Dr Tison: Has received research grants from Janssen Pharmaceuticals Inc. Dr DeMarco: Johnson & Johnson/Actelion: Consultant, speaker, advisory boards, steering committee member for a global study, DSMB member for US trial; United Therapeutics: Adjudication committee member; Acceleron: Research funding for multi center trial; SCOPE/Bial: Data, safety and monitoring board member. All authors have approved the manuscript.

References

1. Prins KW, Thenappan T. World Health Organization Group I Pulmonary Hypertension: Epidemiology and Pathophysiology. Cardiol Clin. 2016;34(3):363–74. [PubMed: 27443134]
2. Hoeper MM, Humbert M, Souza R, Idrees M, Kawut SM, Sliwa-Hahnle K, et al.A global view of pulmonary hypertension. Lancet Respir Med. 2016;4(4):306–22. [PubMed: 26975810]
3. Buckberg G, Hoffman JI. Right ventricular architecture responsible for mechanical performance: unifying role of ventricular septum. J Thorac Cardiovasc Surg. 2014;148(6):3166–71e1–4. [PubMed: 24973008]
4. Nielsen E, Smerup M, Agger P, Frandsen J, Ringgard S, Pedersen M, et al.Normal right ventricular three-dimensional architecture, as assessed with diffusion tensor magnetic resonance imaging, is preserved during experimentally induced right ventricular hypertrophy. Anat Rec (Hoboken). 2009;292(5):640–51. [PubMed: 19306437]
5. Ventetuolo CE, Klinger JR. Management of acute right ventricular failure in the intensive care unit. Ann Am Thorac Soc. 2014;11(5):811–22. [PubMed: 24828526]
6. Thenappan T, Prins KW, Pritzker MR, Scandurra J, Volmers K, Weir EK. The Critical Role of Pulmonary Arterial Compliance in Pulmonary Hypertension. Ann Am Thorac Soc. 2016;13(2):276–84. [PubMed: 26848601]
7. Lammers S, Scott D, Hunter K, Tan W, Shandas R, Stenmark KR. Mechanics and Function of the Pulmonary Vasculature: Implications for Pulmonary Vascular Disease and Right Ventricular Function. Comprehensive Physiology2012.
8. Mahapatra S, Nishimura RA, Sorajja P, Cha S, McGoon MD. Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. J Am Coll Cardiol. 2006;47(4):799–803. [PubMed: 16487848]
9. Campo A, Mathai SC, Le Pavec J, Zaiman AL, Hummers LK, Boyce D, et al.Hemodynamic predictors of survival in scleroderma-related pulmonary arterial hypertension. Am J Respir Crit Care Med. 2010;182(2):252–60. [PubMed: 20339143]
10. Sugimoto K, Yoshihisa A, Nakazato K, Jin Y, Suzuki S, Yokokawa T, et al.Pulmonary Arterial Capacitance Predicts Cardiac Events in Pulmonary Hypertension Due to Left Heart Disease. PLoS One. 2016;11(11):e0165603. [PubMed: 27875533]
11. Al-Naamani N, Preston IR, Hill NS, Roberts KE. The prognostic significance of pulmonary arterial capacitance in pulmonary arterial hypertension: single-center experience. Pulm Circ. 2016;6(4):608–10. [PubMed: 28090304]
12. Dragu R, Rispler S, Habib M, Sholy H, Hammerman H, Galie N, et al.Pulmonary arterial capacitance in patients with heart failure and reactive pulmonary hypertension. Eur J Heart Fail. 2015;17(1):74–80. [PubMed: 25388783]
13. Leuchte HH, Ten Freyhaus H, Gall H, Halank M, Hoeper MM, Kaemmerer H, et al.Risk stratification strategy and assessment of disease progression in patients with pulmonary arterial hypertension: Updated Recommendations from the Cologne Consensus Conference 2018. Int J Cardiol. 2018;272S:20–9. [PubMed: 30266353]
14. Papolos A, Fan E, Wagle RR, Foster E, Boyle AJ, Yeghiazarians Y, et al.Echocardiographic determination of pulmonary arterial capacitance. Int J Cardiovasc Imaging. 2019.
15. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al.Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010;23(7):685–713; quiz 86–8. [PubMed: 20620859]

16. Abbas AE, Franey LM, Marwick T, Maeder MT, Kaye DM, Vlahos AP, et al.Noninvasive assessment of pulmonary vascular resistance by Doppler echocardiography. J Am Soc Echocardiogr. 2013;26(10):1170–7. [PubMed: 23860092]

17. Pellegrini P, Rossi A, Pasotti M, Raineri C, Cicoira M, Bonapace S, et al.Prognostic relevance of pulmonary arterial compliance in patients with chronic heart failure. Chest. 2014;145(5):1064–70. [PubMed: 24356904]

18. Al-Naamani N, Preston IR, Paulus JK, Hill NS, Roberts KE. Pulmonary Arterial Capacitance Is an Important Predictor of Mortality in Heart Failure With a Preserved Ejection Fraction. JACC Heart Fail. 2015;3(6):467–74. [PubMed: 26046840]

19. Dupont M, Mullens W, Skouri HN, Abrahams Z, Wu Y, Taylor DO, et al.Prognostic role of pulmonary arterial capacitance in advanced heart failure. Circ Heart Fail. 2012;5(6):778–85. [PubMed: 23087402]

20. Mahapatra S, Nishimura RA, Oh JK, McGoon MD. The prognostic value of pulmonary vascular capacitance determined by Doppler echocardiography in patients with pulmonary arterial hypertension. J Am Soc Echocardiogr. 2006;19(8):1045–50. [PubMed: 16880101]

21. Tedford RJ. Determinants of right ventricular afterload (2013 Grover Conference series). Pulm Circ. 2014;4(2):211–9. [PubMed: 25006440]

22. Ghio S, Schirinzi S, Pica S. Pulmonary arterial compliance: How and why should we measure it?Glob Cardiol Sci Pract. 2015;2015(4):58. [PubMed: 26779530]

23. Farber HW, Miller DP, McGoon MD, Frost AE, Benton WW, Benza RL. Predicting outcomes in pulmonary arterial hypertension based on the 6-minute walk distance. J Heart Lung Transplant. 2015;34(3):362–8. [PubMed: 25312386]

24. Al-Naamani N, Palevsky HI, Lederer DJ, Horn EM, Mathai SC, Roberts KE, et al.Prognostic Significance of Biomarkers in Pulmonary Arterial Hypertension. Ann Am Thorac Soc. 2016;13(1):25–30. [PubMed: 26501464]

25. Grapsa J, Pereira Nunes MC, Tan TC, Cabrita IZ, Coulter T, Smith BC, et al.Echocardiographic and Hemodynamic Predictors of Survival in Precapillary Pulmonary Hypertension: Seven-Year Follow-Up. Circ Cardiovasc Imaging. 2015;8(6).

Highlights

- Echocardiographic pulmonary arterial compliance predicts outcomes in pulmonary hypertension.
- It outperforms other standard invasive, echocardiographic, and functional markers.
- It was obtainable by echocardiography in >80% of patients in our cohort.

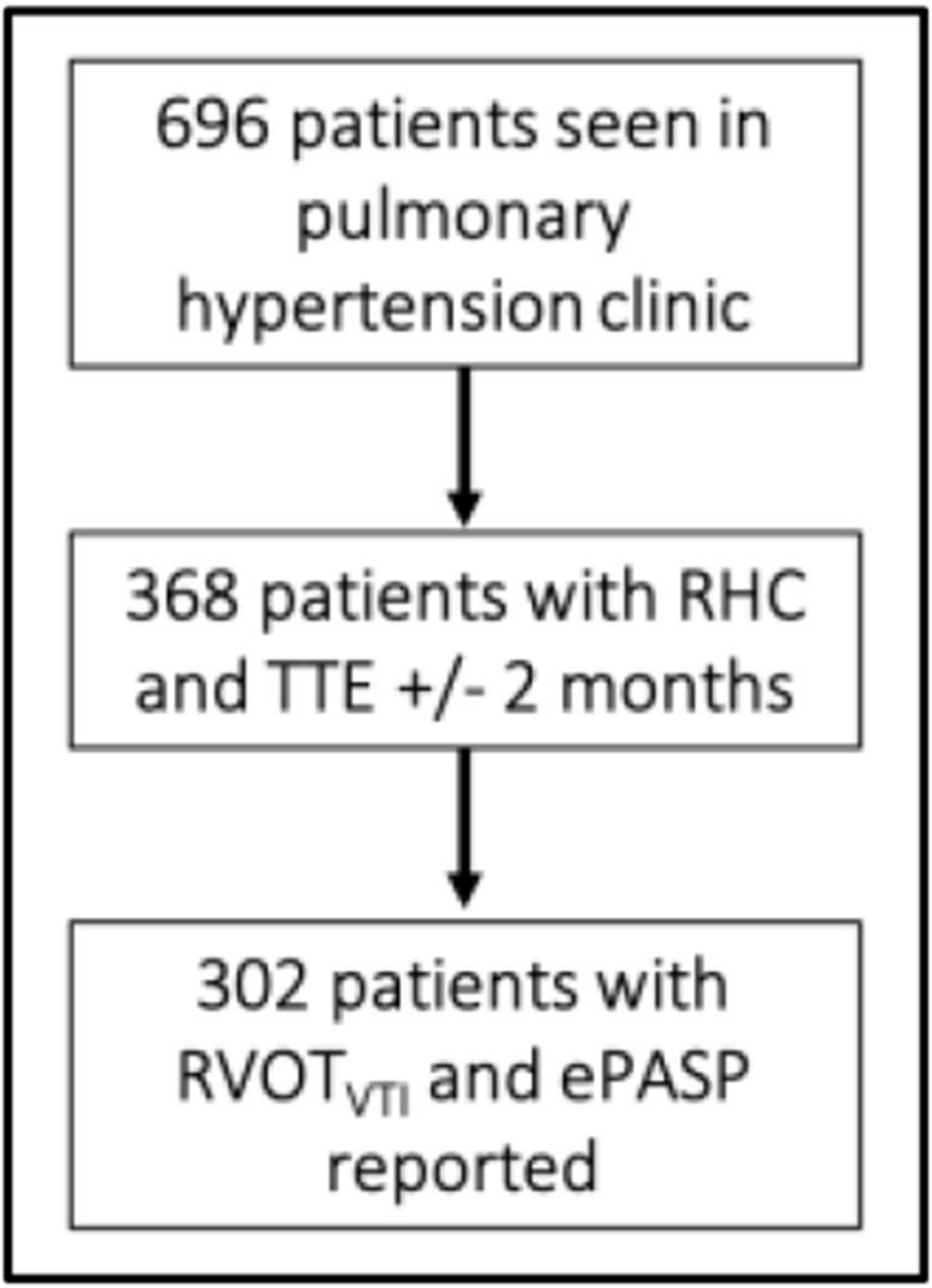

Figure 1. Consort diagram of study participants.

Out of the 696 pulmonary hypertension clinic patients screened, 368 had a right heart catheterization (RHC) performed within 2 months of a transthoracic echocardiography (TTE). The right ventricular outflow tract velocity time integral ($RVOT_{VTI}$) and the pulmonary arterial systolic pressure (ePASP) were both available in 302 of these patients, who were included in the present study.

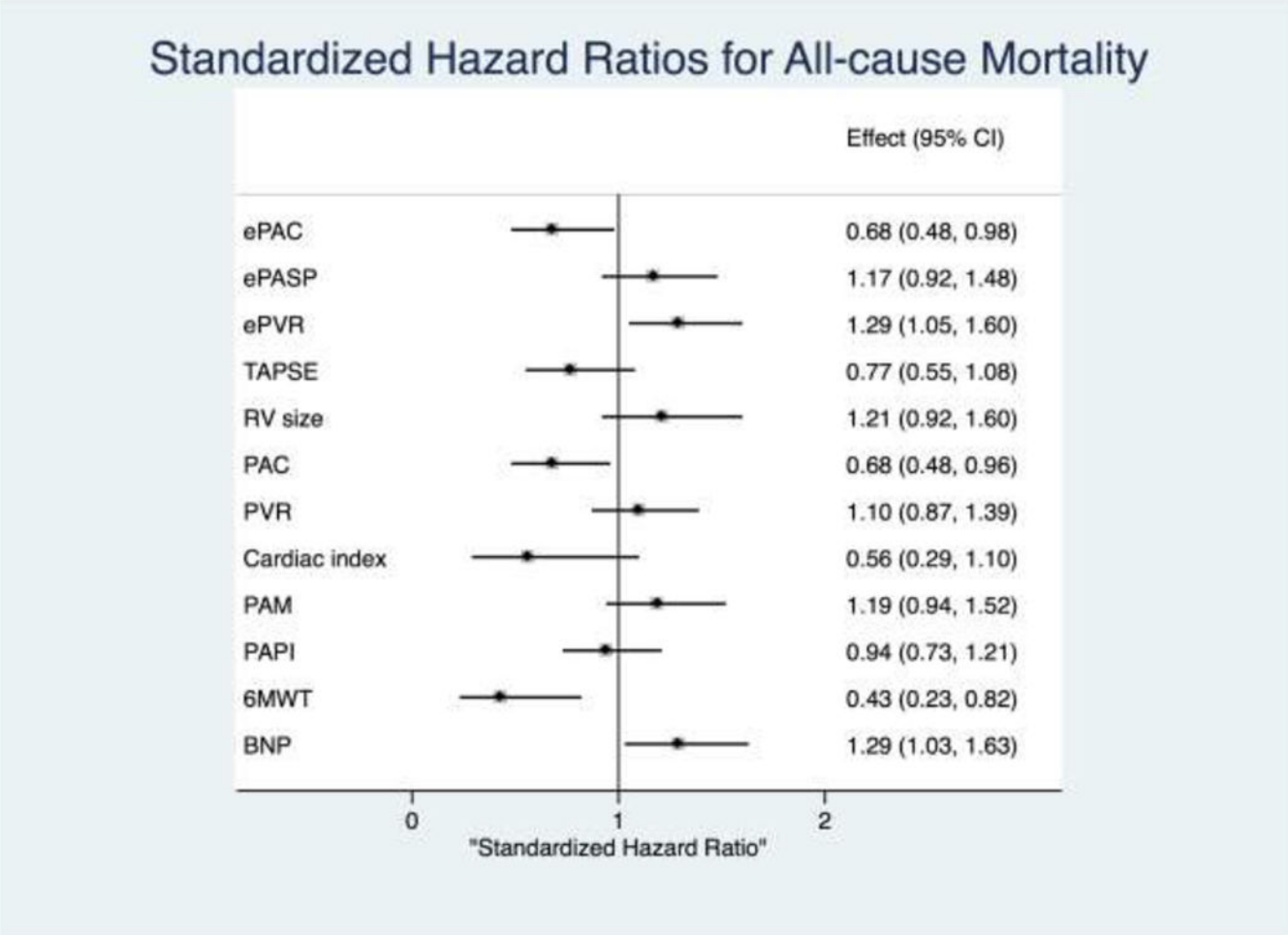

Figure 2. Hazard ratios for predictors of all-cause mortality in pulmonary hypertension.

ePAC, right ventricular outflow tract velocity time integral to pulmonary arterial systolic pressure ratio; ePASP, pulmonary arterial systolic pressure; ePVR, echocardiographic pulmonary vascular resistance; TAPSE, tricuspid annular planar systolic excursion; RV size, right ventricular size; PAC, pulmonary arterial capacitance. PVR, pulmonary vascular resistance; PAM, mean pulmonary artery pressure; PAPI, pulmonary arterial pulsatility index; 6MWT, six-minute walk distance (meters); BNP, B-type natriuretic peptide.

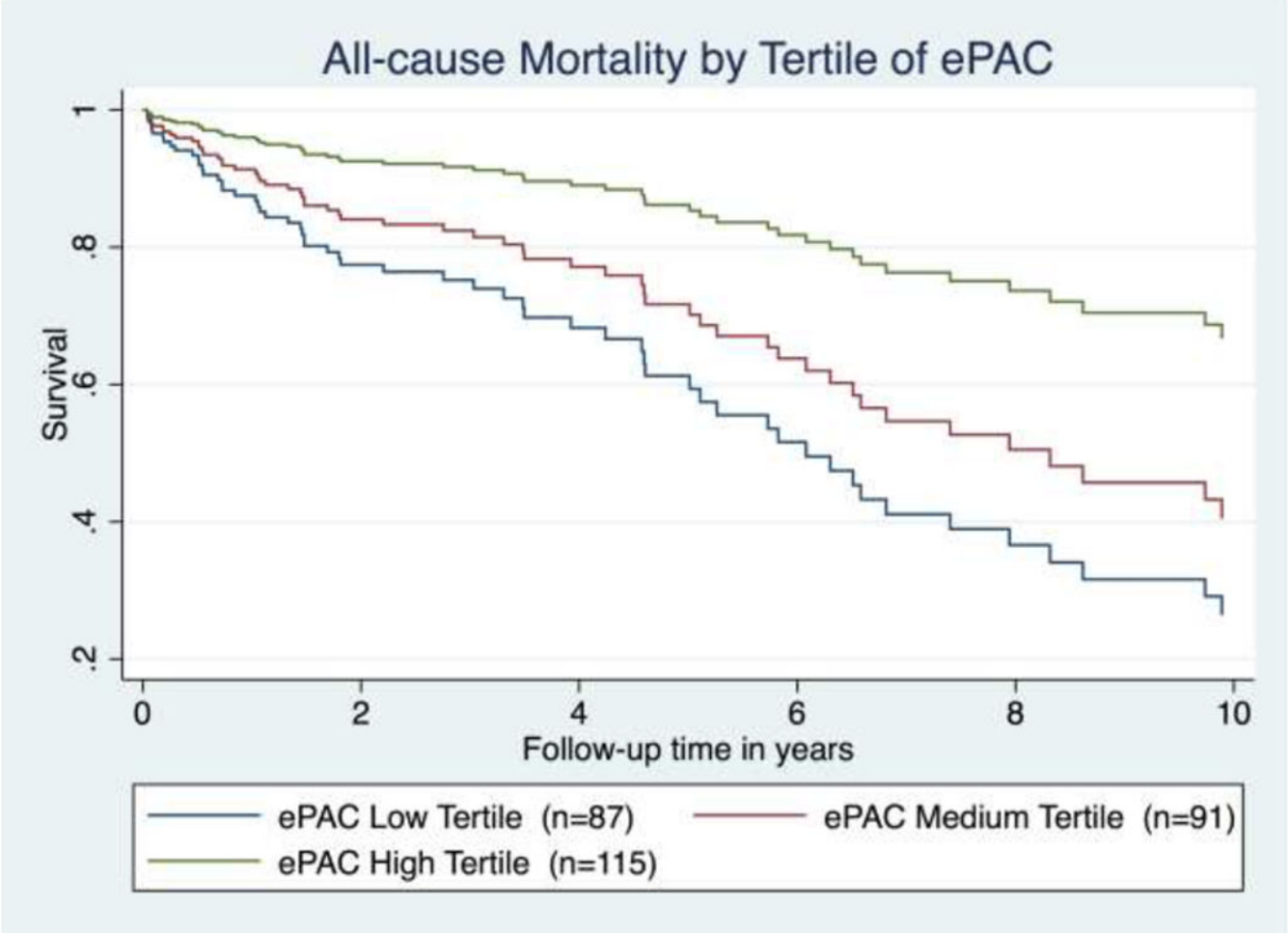

Figure 3. All-cause mortality by tertiles of echocardiographic pulmonary arterial capacitance.
ePAC tertiles defined as low <0.15 (n=87), medium 0.15-0.25 (n=91), and high >0.25 (n=115). ePAC, right ventricular outflow tract velocity time integral to pulmonary arterial systolic pressure ratio.

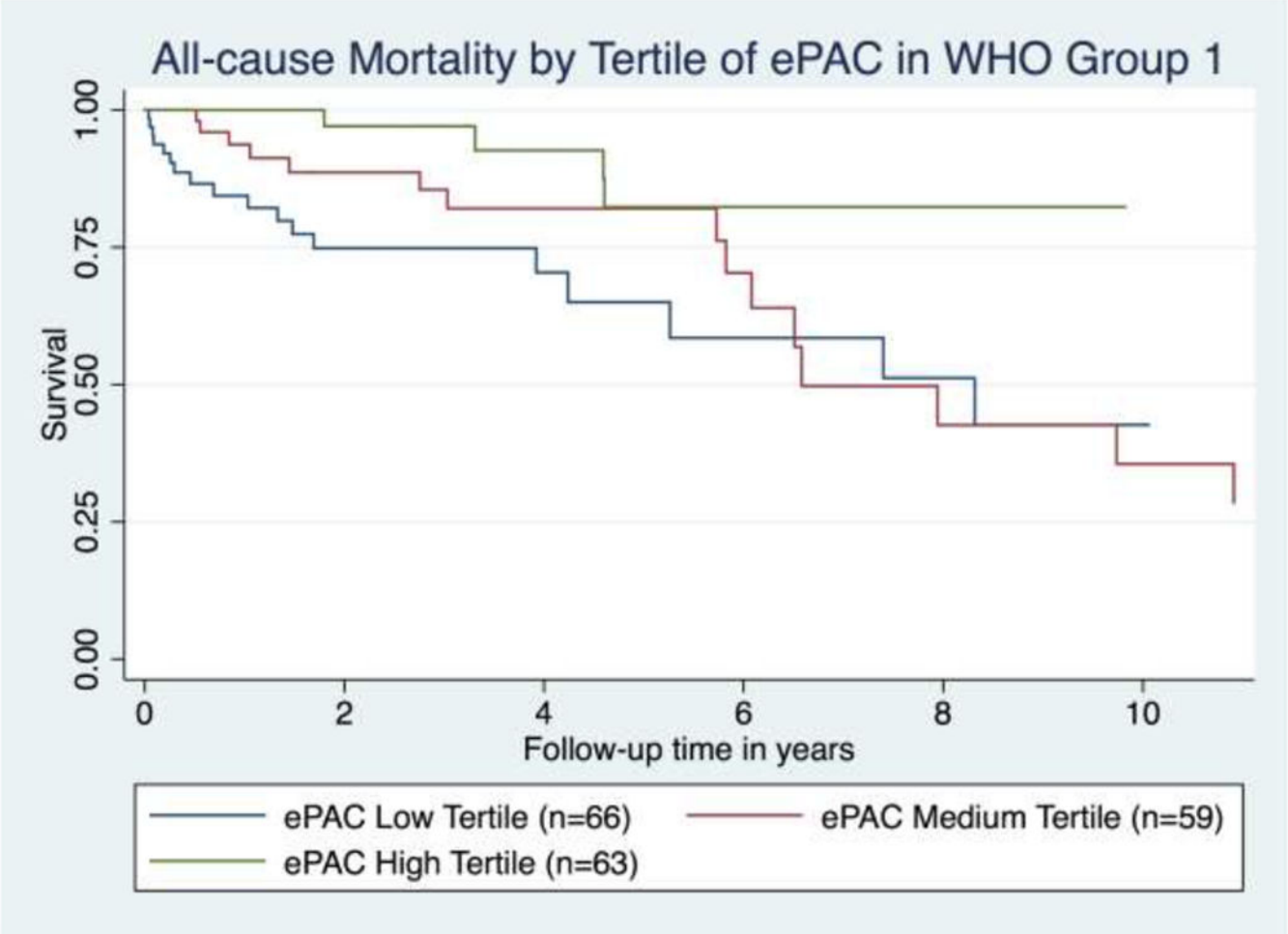

Figure 4. All-cause mortality by tertiles of echocardiographic pulmonary arterial capacitance in those with WHO Group 1 pulmonary hypertension.

ePAC tertiles defined as low <0.15 (n=66), medium 0.15-0.25 (n=59), and high >0.25 (n=63). ePAC, right ventricular outflow tract velocity time integral to pulmonary arterial systolic pressure ratio.

Table 1

Cohort Description.

	N / %
Age, years (SD)	55 +/− 14.5
Female	204 (68%)
HFpEF	59 (20%)
HFrEF	31 (10%)
Ischemic	55 (18%)
WHO functional class	
1	15 (6%)
2	63 (25%)
3	134 (52%)
4	45 (17%)
WHO group	
1	196 (65%)
2	44 (15%)
3	28 (9%)
4	17 (6%)
5	6 (2%)
PDE-5I	137 (45%)
ERA	68 (23%)
Prostacyclin	44 (15%)
HTN	144 (48%)
HLD	82 (27%)
CKD	68 (23%)
DM	58 (19%)
AF/AFL	56 (19%)
Obesity	64 (21%)
Smoking history	127 (42%)

	N / %
COPD	42 (14%)
OSA	81 (27%)
Systolic blood pressure (mmHg) (SD)	123 +/− 23
Diastolic blood pressure (mmHg) (SD)	68 +/− 12.7
Heart Rate (BPM) (SD)	77 +/− 15.7
BNP (pg/ml) (range)	402 +/− 557
Echocardiographic Variables	
LVEF (%) (SD)	64% +/− 10%
$RVOT_{VTI}$ (cm) (SD)	18.9 +/− 1.4
ePASP (mmHg) (SD)	68.7 +/− 23.6
TAPSE (cm) (SD)	1.9 +/− 0.6
ePAC (cm/mmHg) (SD)	0.3 +/− 0.2
ePVR (Wood units) (SD)	6.3 +/− 4.2
Right Heart Catheterization Hemodynamics	
RAP (mmHg) (SD)	8.6 +/− 5.6
PAM (mmHg) (SD)	42.9 +/− 13.6
PCWP (mmHg) (SD)	11.4 +/− 5.9
Fick cardiac index (L/min/m2) (SD)	2.8 +/− 2.3
Fick PVR (Wood units) (SD)	7.9 +/−5.3
Pulmonary arterial capacitance (mL/mmHg) (SD)	1.9 +/− 1.4
Pulmonary arterial pulsatility index (SD)	7.4 +/−7.2

SD, standard deviation; HFpEF, heart failure preserved ejection function; HFrEF, heart failure reduced ejection function; WHO, World Health Organization; PDE-5I, phosphodiesterase-5 inhibitor; ERA, endothelin receptor antagonist; CAD, coronary artery disease; HLD, hyperlipidemia; CKD, chronic kidney disease; DM, diabetes mellitus; AF/AFL, atrial fibrillation/atrial flutter; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; $RVOT_{VTI}$, right ventricular outflow tract velocity time integral; ePASP, pulmonary arterial systolic pressure; TAPSE, tricuspid annular planar systolic excursion; ePAC, right ventricular outflow tract velocity time integral to pulmonary arterial systolic pressure ratio; ePVR, echocardiographic pulmonary vascular resistance; RAP, right atrial pressure; PAM, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.

Table 2

Multivariable-adjusted Hazard Ratios for All-cause Mortality.

Predictor	Hazard Ratio (95% Confidence Interval)	*p*-value
ePAC (standardized)	0.65 (0.45-0.95)	**0.027**
Age	1.01 (0.99-1.03)	0.391
Gender (Female)	1.52 (0.84-2.73)	0.164
Coronary Artery Disease	1.03 (0.52-2.06)	0.922
Hypertension	0.98 (0.56-1.72)	0.949
Diabetes	0.94 (0.52-1.85)	0.940
Obesity	1.36 (0.75-2.47)	0.311
Smoking history	1.65 (0.92-2.97)	0.094
Chronic Obstructive Pulmonary Disease	1.14 (0.51-2.53)	0.757

ePAC, right ventricular outflow tract velocity time integral to pulmonary arterial systolic pressure ratio.

p-values bold for <0.05.