Published in final edited form as:

Crit Care Med. 2017 March ; 45(3): 422–429. doi:10.1097/CCM.0000000000002186.

Pulmonary arterial compliance in ARDS: clinical determinants and association with outcome from the FACTT cohort

Thomas S. Metkus, MD[1], **Emmanouil Tampakakis, MD**[1], **Christopher J Mullin, MD**[2], **Brian A. Houston, MD**[1], **Todd M. Kolb, MD, PhD**[2], **Stephen C. Mathai, MD**[2], **Rachel Damico Maron, MD PhD**[2], **Bradley A Maron, MD**[3], **Paul M. Hassoun, MD**[2], **Roy G. Brower, MD**[2], and **Ryan J. Tedford, MD**[1]

[1]Division of Cardiology, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA

[2]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA

[3]Department of Medicine, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; Department of Cardiology, Boston VA Healthcare System, Boston, Massachusetts, USA

Abstract

Objective—Pulmonary vascular dysfunction is associated with adverse prognosis in patients with the acute respiratory distress syndrome (ARDS), however the prognostic impact of pulmonary arterial compliance (C_{PA}) in ARDS is not established.

Design, Setting, Patients—We performed a retrospective analysis of 363 subjects with ARDS who had complete baseline right heart catheterization data from the Fluid and Catheter Treatment Trial (FACTT) to test whether C_{PA} at baseline and over the course of treatment predicted mortality.

Main Results—Baseline C_{PA} (HR 1.18 per interquartile range [IQR] of 1/ C_{PA}, 95% CI 1.02-1.37; p=0.03) as well as pulmonary vascular resistance (PVR) (HR 1.28 per IQR, 95% CI 1.07-1.53; p=0.006) both modestly predicted 60-day mortality. Baseline C_{PA} remained predictive of mortality when PVR was in the normal range (p=0.02). Between day 0 and day 3, C_{PA} increased in ARDS survivors and remained unchanged in non-survivors, while PVR did not change in either group. The resistance-compliance product (RC time) increased in survivors compared to non-survivors, suggesting improvements in RV load.

Conclusion—Baseline measures of C_{PA} and PVR predict mortality in ARDS, and C_{PA} remains predictive even when PVR is normal. C_{PA} and RV load improve over time in ARDS survivors. Future studies should assess the impact of RV protective ARDS treatment on RV afterload and outcome.

Corresponding Author and reprints: Ryan J. Tedford, MD, Assistant Professor of Medicine, Johns Hopkins School of Medicine, 7125A Zayed; 1800 Orleans St, Baltimore, MD 21287, Ryan.Tedford@jhmi.edu.

Author contributions: TM and RJT 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. ET, CM, BAH, TMK, SCM, RD, PMH, BAM and RGB contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript including critical revision.

Keywords

ARDS; pulmonary arterial compliance; pulmonary vascular resistance; pulmonary vascular disease

Background

The acute respiratory distress syndrome (ARDS) is associated with substantial morbidity and mortality (1-3), and refined risk stratification of ARDS patients is needed. ARDS-associated right heart failure has been associated with poor outcome in some (4, 5) but not all (6) studies. Markers of static right ventricular (RV) afterload such as pulmonary vascular resistance (PVR) may predict adverse outcome (7) but do not account for the pulsatile nature of blood flow and wave reflections that contribute to RV afterload. Pulmonary arterial compliance (C_{PA}) is a major component of RV pulsatile load, which is related both to PVR and left heart filling pressures (8, 9) and may also better characterize RV load when PVR is in the normal range (8, 10). Lower C_{PA} has been associated with mortality in both pulmonary arterial hypertension and left heart failure (9-12), but has not been studied in ARDS. Given a possible important role of fluid balance and cardiac filling pressure in mitigating outcome in ARDS (13-16), we hypothesized that C_{PA} would predict mortality in patients with ARDS. We also sought to characterize the relationship of C_{PA} and PVR in ARDS and to determine clinical factors associated with both C_{PA} and PVR.

Methods

Patient population

The Fluid and Catheter Treatment Trial (FACTT) was conducted by the ARDS Network. The trial randomized 1000 subjects with ARDS in a 2x2 factorial design to placement of either central venous catheter or pulmonary artery catheter and to either a conservative or liberal fluid management strategy (15, 17). Patients were receiving low tidal volume mechanical ventilation and had a PaO2/FIO_2 ratio less than 300 and bilateral infiltrates not referable to hydrostatic edema, which was assessed clinically (15, 17). Patients with myocardial infarction within the prior 30 days and severe chronic lung disease were excluded from trial enrollment.

We obtained the trial dataset via the NIH BioLINCC data repository (18). Five hundred thirteen patients were randomized to pulmonary artery catheter placement. Of these, 146 subjects were excluded due to lack of complete hemodynamic or clinical data (baseline systolic pulmonary artery pressure [SPAP], diastolic pulmonary artery pressure [DPAP], pulmonary artery wedge pressure [PAWP], cardiac index [CI], heart rate, height, and weight were required). In addition, 4 subjects were excluded because recorded hemodynamics generated a negative value for PVR. Therefore, 363 subjects with complete day 0 right heart catheterization data were included in this study. Cardiac filling pressures were measured with subjects supine at end-expiration based on ventilator pressure waveforms by study investigators (17). Cardiac output was measured by thermodilution (17). The study was approved by institutional review boards (IRB) at participating centers. The Johns Hopkins

IRB approved this analysis for exempt status given that all datasets were anonymized at time of receipt.

Markers of pulmonary vascular function

PVR was calculated with the standard formula: (mean PA pressure [mPAP] - PAWP)/cardiac output (CO). C_{PA} was calculated as stroke volume (SV) divided by PA pulse pressure (8). The RC time is the product of C_{PA} and PVR. In survival analyses, compliance was represented as the inverse of compliance ($1/C_{PA}$) so that the effect was directionally comparable to that of PVR.

Statistics

Baseline characteristics and hemodynamics were compared using Chi-square, Student's T test or Wilcoxon rank-sum as appropriate. Non-linear regression was performed to identify the best-fit hyperbolic curve for C_{PA} as a function of PVR (the RC curve). Separate RC curves were constructed for those subjects with PAWP < 12 mmHg (lowest quartile of PAWP) and > 19 mmHg (highest quartile of PAWP). These curves were compared after log-log transformation with analysis of covariance (ANCOVA). The association of $1/C_{PA}$ and PVR with death was investigated with Cox Proportional Hazard models. The proportional hazards assumption was met in all cases. Adjusted Cox models were then performed forcing in APACHE III score as a covariate. Receiver operator curves were constructed to compare the area under the curve for the association of PVR and $1/C_{PA}$ with death and to determine the optimal cut-point for both PVR and $1/C_{PA}$ using the method of Youden. Survival analysis was then performed using methods of Kaplan-Meier for $1/C_{PA}$ and PVR at the identified optimal cut-point. Single linear regression was performed to determine associations of clinical variables with C_{PA} and PVR. A two-tailed P value of less than 0.05 was considered statistically significant. All analyses were performed using StataSE version 14.

Results

Demographic, clinical and physiologic data are shown in Table 1. Compared with survivors, those who died were older, less likely to be Caucasian, had lower BSA, were more likely to be on vasopressors, and had higher APACHE III scores. Those who died had worse hemodynamic profiles including lower systemic blood pressures, higher heart rate and elevated markers of RV afterload (Table 2).

Demographic and clinical factors associated with C_{PA} and PVR are summarized in Supplemental E-table 1. Clinical factors associated with both C_{PA} and PVR included age, heart rate, BSA, and A-a gradient ($p<0.05$ for all). Lower body temperature (β -0.13, SE 0.06, p=0.01) and higher ventilator driving pressure (β 0.14, SE 0.01, p=0.02) were associated with higher PVR but neither factor was associated with C_{PA}. Lower arterial pH (β 0.11, SE 0.14, p=0.04) was associated with lower C_{PA} but not associated with PVR. Positive fluid balance (β -0.13, SE 0.0009, p=0.01) was associated with lower C_{PA} but not associated with PVR.

As expected, PVR and C_{PA} were related in an inverse hyperbolic manner (Figure 1, panel A). Elevated left heart filling pressure resulted in a downward shift of the RC curve consistent with lower C_{PA} at a given PVR, as shown in Figure 1, panel B ($P < 0.0001$ for comparison of curves after log-log transformation). Although higher PAWP lowered C_{PA} at a given PVR, higher PAWP on day 0 was associated with a reduced risk of death (HR 0.96 per mmHg: 95% CI 0.93-1.0; P = 0.03).

Baseline C_{PA} and PVR were modestly associated with death in univariate models (HR 2.84 [95% CI 1.12-7.17 per unit] and 1.18 [95% CI 1.02-1.37 per IQR increase] for C_{PA}, p = 0.03; HR 1.20 [95%CI 1.06-1.36 per unit] and 1.28 [95% CI 1.07-1.53 IQR increase] for PVR, p =0.006). After adjusting for APACHE III score, PVR remained a significant predictor of mortality (HR 1.26, 95% CI 1.05-1.5, p=0.01) while only a trend remained for C_{PA} (HR 1.15, 95% CI 0.99-1.34, p=0.07). These findings were not mediated solely by cardiac output nor stroke volume- in univariate analyses, neither cardiac output (HR 0.91 per IQR increase, 95% CI 0.70-1.18, p=0.5) nor stroke volume (HR 0.78 per increase in IQR, 95% CI 0.60-1.02, p=0.07) was associated with mortality. The borderline association of mortality with stroke volume attenuated when adjusting for APACHE score (HR 0.88 per increase in IQR, 95% CI 0.68-1.14, p=0.3).

The area under the ROC curve for $1/C_{PA}$ to predict 60-day death was 0.60 compared to 0.58 for PVR (P =0.4). The optimal cut-point to predict death for $1/C_{PA}$ was 0.30 mmHg/mL (3.33 mmHg/mL for C_{PA}), which was 47% sensitive and 73% specific. The optimal cut-point to predict death for PVR was 1.91 WU, which was 46% sensitive and 68% specific. Figure 2 demonstrates Kaplan-Meier curves for PVR and $1/C_{PA}$ dichotomized at these cut-points. In an analysis of the subset of the cohort with baseline PVR less than 3 WU (N=301 of 363), $1/C_{PA}$ greater than the predetermined optimal cut point remained associated with mortality (P = 0.02; e-Figure), although PVR did not (P = 0.2). In the PVR <3 WU cohort, subjects with lower C_{PA} had lower stroke volume and lower cardiac index but similar PAWP (supplemental e-table 2) than those with higher C_{PA}.

Figure 3 panels A and B display the trends in mean PVR and C_{PA} over the first 4 complete trial days (days 0, 1, 2, and 3) for subjects with available data. At trial enrollment, subjects who ultimately died had lower baseline C_{PA}, and C_{PA} did not change over the first 4 trial days (P = 0.9). Subjects who ultimately lived had higher baseline C_{PA} and C_{PA} increased over the first 4 trial days (P = 0.02), and an increasing C_{PA} was therefore associated with a lower likelihood of death (HR 0.58, 95% CI 0.37-0.91; P = 0.02) Subjects who ultimately died had higher baseline PVR, which did not change over the first 4 trial days (P=0.6). Consequently, the RC time increased in survivors (P=0.02) yet remained unchanged in non-survivors, suggesting that survivors had less RV pulsatile load for a given PVR. Survivors also demonstrated decreasing heart rate, increasing stroke volume, and lower right atrial pressure, pulmonary artery pressure, and PAWP between day 0 and day 3 (supplemental E Table 3). The median cumulative fluid balance in survivors was positive 1.2 L (IQR -2.4 – +5.7 L) versus positive 5.6 L (IQR +1.8 - + 11.6 L) in non-survivors (P = 0.0001). There were no differences in assignment to a conservative fluid management strategy between the survivors and non-survivors (48% v. 43%, P = 0.5).

Discussion

Major Findings

In this analysis of a modern ARDS cohort from FACTT, C_{PA}- a marker of pulsatile RV afterload- and PVR- a marker of static RV afterload- are both modestly associated with 60-day all-cause mortality, and C_{PA} remains predictive even when PVR is in the normal range. C_{PA} and PVR are related in an inverse hyperbolic fashion, consistent with other disease states. The pulmonary vascular RC curve in ARDS is sensitive to left heart filling pressure, and elevated PAWP lowers compliance independent of resistance which is anticipated and consistent with observations in other disease states. Finally, we demonstrate that C_{PA} increases over time in patients who survive their ARDS while remaining constant in non-survivors.

RC relationship in ARDS

We demonstrate for the first time in mechanically ventilated ARDS patients, that C_{PA} and PVR follow an inverse hyperbolic relationship. Pulmonary hypertension associated with respiratory failure was first described by Zapol and Snider (19), and since then the dependence of C_{PA} on PVR has been suggested in a number of studies including those with normal subjects (20), known or suspected pulmonary hypertension (8, 20, 21), and interstitial lung disease (8). This concept was perhaps best illustrated by Newman and colleagues who administered inhaled nitric oxide to subjects with vasoreactive PAH (22), demonstrating with falling PVR, C_{PA} increased in a predictable fashion, with little impact on the RC time. A consequence of this RC relationship is that in order to reduce pulsatile RV load, PVR must be lowered to the steep portion of the RC curve (e.g. 1-3 WU). Small changes in PVR could dramatically impact C_{PA}, potentially making C_{PA} a better discriminator of RV load and survival in this range of PVR.

C_{PA} in ARDS

Baseline C_{PA} was associated with 60-day mortality in ARDS although it was not a clearly superior prognostic marker compared to PVR. PVR has been previously shown to predict mortality in the FACTT cohort by Bull and colleagues using different methodology (7). The association of C_{PA} with mortality attenuated when adjusted for APACHE score, whereas the association of PVR did not. Our finding that C_{PA} was associated not only with fluid balance, but also with acidosis, hypoxia, and tachycardia (variables included in APACHE) suggests that either C_{PA} is more affected by variables associated with illness severity than PVR or that lower compliance itself impacts illness severity. Higher PAWP predictably decreased C_{PA} at a given resistance. In this cohort, lower day 0 PAWP was associated with mortality. This “protective” association of higher PAWP could be a marker of more severe systemic vasodilatation, third spacing and hence more severe hemodynamic compromise among those with low PAWP. This relationship contrasts with left heart failure where elevation in PAWP (and lower compliance) is pathogenic. This could explain why baseline C_{PA} was not clearly superior to PVR in predicting mortality as factors other than RV load impacted outcome.

Compliance was predictive of mortality in subjects with PVR < 3WU whereas PVR was not. Pellegrini also found C_{PA} remained associated with mortality even when PVR was in the

normal range in a cohort of left heart failure patients (10). Our results also follow from studies that have demonstrated the prognostic utility of estimated pulmonary arterial compliance in other disease states such as heart failure and primary pulmonary hypertension (9, 11, 12, 23). There were no differences in baseline PAWP between survivors and non-survivors in the PVR < 3WU cohort despite differences in C_{PA}. Because left heart pressures impacted baseline compliance less in our cohort, these findings may speak more to the impact of small changes in PVR on compliance and total RV load (i.e. steepness of the RC curve).

We also found an increase in C_{PA} during the study time course was associated with survival although PVR did not change dramatically in this group. The change in C_{PA} was mediated at least in part by reduction in PAWP and less positive fluid balance. In a recent analysis from the FACTT data set, it was noted that among patients with lower filling pressures at baseline, a fluid conservative strategy was associated with benefit (13). Other studies in ARDS and critical illness have supported these findings as well (13, 24, 25). Avoiding positive fluid balance, when possible, should result in higher C_{PAdyn} and reduce pulsatile RV afterload.

Therapeutic implications

Our findings represent associations of PVR and C_{PA} with outcome, and it cannot be presumed that pulmonary vascular dysfunction causes increased mortality directly in this setting. Nonetheless, these associations should contribute to hypotheses regarding therapeutic implications of targeting pulmonary vascular dysfunction in ARDS. Although total RV load in the setting of a normal PVR likely remains modest, even when C_{PA} is depressed, recent work has demonstrated that even borderline elevations in load may impact mortality (26). Modifying RV load therapeutically in ARDS has not been well studied. Trials assessing inhaled nitric oxide (iNO) in ARDS have shown no improvement in outcome (27, 28) at a median dose across trials of 10 ppm. However, there is heterogeneity in both the oxygenation response and the hemodynamic response to iNO in ARDS, both between patients and over time within the same patient (29), and patients who respond to iNO have lower treatment-related PVR than non-responders (30). The impact of pulmonary vasodilators on right heart hemodynamics and the subsequent impact on outcome needs additional study.

An “RV protective” approach to mechanical ventilation in ARDS has been proposed (31-34) which incorporates limiting plateau pressure, avoiding respiratory acidosis, and titrating ventilator parameters to an endpoint of adequate RV function assessed with echocardiography. While the clinical effect of this approach on RV afterload has not been demonstrated prospectively, our results confirm that these components of RV protection- including ventilator driving pressure and acidosis- are indeed associated with PVR and C_{PA}, and that fluid balance also plays an important role. Our results suggest that optimization of heart rate in patients with arrhythmia, avoidance of hypothermia (suggested by our study and others to increase pulmonary vascular resistance (35)), and avoiding positive fluid balance should be assessed in future studies of RV protection in ARDS. Our findings could contribute to the design of an RV protective approach to mechanical ventilation that should be evaluated prospectively. Although right heart catheterization use in ARDS is declining

(36), hemodynamics including C_{PA} can be estimated by echocardiography (37) and echo-estimated C_{PA} is prognostic in PAH (11). Longitudinal tracking of C_{PA} with echocardiography is an attractive strategy in ARDS, and should be investigated in prospective trials.

Limitations

This is a retrospective, observational study, and, thus, our findings are hypothesis generating and represent associations only. As such, causality cannot be inferred from relationships reported in this study. For example, it is not possible to determine if changes in C_{PA} promote worsening hemodynamics, RV function and survival, or is simply a marker of illness severity. The specific cause of death was not available for this cohort, and, therefore, it was not possible to determine if patients died of RV failure or other causes. Few patients in our cohort were treated with prone positioning which has been demonstrated to have beneficial hemodynamic effects (38) This analysis is a hemodynamic analysis, whereas much of the literature defining the relationship between ARDS, outcome, and *cor pulmonale* relies on echocardiography findings (5, 31, 33, 34). Future studies should assess the echocardiographic correlates of C_{PA} and PVR in ARDS enabling non-invasive assessment in ARDS. An additional limitation is that SV/PP represents a lumped simplification for compliance and some of this theory has recently been debated (39). Other parameters such as pulmonary artery elastance are also important lumped parameters of RV afterload, although they too have limitations and how to best estimate pulmonary artery elastance remains controversial (40). Hemodynamic measurements were made by study investigators at the bedside after formal hemodynamic assessment training. Although interpretation of hemodynamics may be variable among examiners even with training, we believe this likely represents a best case scenario for clinical practice. Even with variability, the changes in compliance and association with outcome were statistically significant, and measurement error likely would bias toward the null. Finally, we necessarily restricted our analysis to only those FACTT subjects with a complete hemodynamic data set at trial enrollment and prior to protocol mandated fluid management. Although it would be prudent to validate these findings in future cohorts, with declining use of the pulmonary artery catheter in ARDS, this will be challenging (36).

In conclusion, we demonstrate an inverse hyperbolic relationship between C_{PA} and PVR in a cohort of patients with ARDS, which is modified by left heart filling pressure. Baseline C_{PA} and PVR both predict mortality, and C_{PA} predicts mortality even when PVR is normal. Improvement in C_{PA} over time is associated with survival. Patient factors including age and heart rate and disease specific clinical factors such as fluid balance and ventilator driving pressure are associated with aspects of right ventricular afterload. Future studies should assess the value of non-invasive assessment of C_{PA} in ARDS as well as the impact of RV protective ARDS treatment on RV afterload and outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Copyright form disclosures: Dr. Metkus received funding from the NHLBI, T32 salary support. He received support for article research from the National Institutes of Health (NIH). Dr. Mathai disclosed: he has served as a consultant for Actelion, Bayer, and Gilead Sciences. Dr. Maron received funding from Gilead Sciences Inc. He received support for article research from the NIH, the American Heart Association, and the Cardiovascular Medical Research and Education Foundation. Dr. Hassoun received funding from Gilead (part of the Scientific Advisory Board, unrelated to the current work). Dr. Tedford received support for article research from the NIH. The remaining authors have disclosed that they do not have any potential conflicts of interest.

Dr. Maron received grant funding from Gilead Sciences. Dr. Mathai received consulting fees from Actelion, Bayer Healthcare and Gilead. Dr. Hassoun serves on the Scientific Advisory Board of Gilead. Dr. Metkus received unrestricted research funds from Abbott Diagnostics to support an investigator-initiated study, received consulting fees from BestDoctors, Inc and Oakstone-EBIX CME unrelated to the current work and is eligible for publishing royalties from McGraw-Hill publishing, unrelated to the current work.

Funding Sources: This study was supported by the NIH - NHLBI (1K08HL11207-01A1, L30 HL110304, T32-HL007227-40), the American Heart Association (AHA 15GRNT25080016), Pulmonary Hypertension Association, Cardiovascular Medical Research and Education Fund (CMREF), and Klarman Foundation at Brigham and Women's Hospital.

References

1. Ware LB, Matthay MA. The acute respiratory distress syndrome. The New England journal of medicine. 2000; 342(18):1334–1349. [PubMed: 10793167]
2. Maybauer MO, Maybauer DM, Herndon DN. Incidence and outcomes of acute lung injury. The New England journal of medicine. 2006; 354(4):416–417. author reply 416-417.
3. Sweatt AJ, Levitt JE. Evolving epidemiology and definitions of the acute respiratory distress syndrome and early acute lung injury. Clinics in chest medicine. 2014; 35(4):609–624. [PubMed: 25453413]
4. Boissier F, Katsahian S, Razazi K, et al. Prevalence and prognosis of cor pulmonale during protective ventilation for acute respiratory distress syndrome. Intensive care medicine. 2013; 39(10): 1725–1733. [PubMed: 23673401]
5. Mekontso Dessap A, Boissier F, Charron C, et al. Acute cor pulmonale during protective ventilation for acute respiratory distress syndrome: prevalence, predictors, and clinical impact. Intensive care medicine. 2015
6. Ryan D, Frohlich S, McLoughlin P. Pulmonary vascular dysfunction in ARDS. Annals of intensive care. 2014; 4:28. [PubMed: 25593744]
7. Bull TM, Clark B, McFann K, et al. Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury. American journal of respiratory and critical care medicine. 2010; 182(9):1123–1128. [PubMed: 20558628]
8. Tedford RJ, Hassoun PM, Mathai SC, et al. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. Circulation. 2012; 125(2):289–297. [PubMed: 22131357]
9. Dupont M, Mullens W, Skouri HN, et al. Prognostic role of pulmonary arterial capacitance in advanced heart failure. Circulation Heart failure. 2012; 5(6):778–785. [PubMed: 23087402]
10. Pellegrini P, Rossi A, Pasotti M, et al. Prognostic relevance of pulmonary arterial compliance in patients with chronic heart failure. Chest. 2014; 145(5):1064–1070. [PubMed: 24356904]
11. Mahapatra S, Nishimura RA, Oh JK, et al. The prognostic value of pulmonary vascular capacitance determined by Doppler echocardiography in patients with pulmonary arterial hypertension. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2006; 19(8):1045–1050. [PubMed: 16880101]
12. Al-Naamani N, Preston IR, Paulus JK, et al. Pulmonary Arterial Capacitance Is an Important Predictor of Mortality in Heart Failure With a Preserved Ejection Fraction. JACC Heart failure. 2015; 3(6):467–474. [PubMed: 26046840]
13. Semler MW, Wheeler AP, Thompson BT, et al. Impact of Initial Central Venous Pressure on Outcomes of Conservative Versus Liberal Fluid Management in Acute Respiratory Distress Syndrome. Critical care medicine. 2016

14. Neamu RF, Martin GS. Fluid management in acute respiratory distress syndrome. Current opinion in critical care. 2013; 19(1):24–30. [PubMed: 23222675]
15. National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials, N. Wiedemann HP, et al. Comparison of two fluid-management strategies in acute lung injury. The New England journal of medicine. 2006; 354(24):2564–2575. [PubMed: 16714767]
16. Sakr Y, Vincent JL, Reinhart K, et al. High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury. Chest. 2005; 128(5):3098–3108. [PubMed: 16304249]
17. National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials N. Wheeler AP, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. The New England journal of medicine. 2006; 354(21):2213–2224. [PubMed: 16714768]
18. Giffen CA, Carroll LE, Adams JT, et al. Providing Contemporary Access to Historical Biospecimen Collections: Development of the NHLBI Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). Biopreservation and biobanking. 2015; 13(4):271–279. [PubMed: 26186276]
19. Zapol WM, Snider MT. Pulmonary hypertension in severe acute respiratory failure. The New England journal of medicine. 1977; 296(9):476–480. [PubMed: 834225]
20. Hadinnapola C, Li Q, Su L, et al. The resistance-compliance product of the pulmonary circulation varies in health and pulmonary vascular disease. Physiological reports. 2015; 3(4)
21. Tedford RJ, Mudd JO, Girgis RE, et al. Right ventricular dysfunction in systemic sclerosis-associated pulmonary arterial hypertension. Circulation Heart failure. 2013; 6(5):953–963. [PubMed: 23797369]
22. Newman JH, Brittain EL, Robbins IM, et al. Effect of acute arteriolar vasodilation on capacitance and resistance in pulmonary arterial hypertension. Chest. 2015; 147(4):1080–1085. [PubMed: 25340330]
23. Mahapatra S, Nishimura RA, Sorajja P, et al. Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. J Am Coll Cardiol. 2006; 47(4):799–803. [PubMed: 16487848]
24. Rosenberg AL, Dechert RE, Park PK, et al. Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort. Journal of intensive care medicine. 2009; 24(1):35–46. [PubMed: 19103612]
25. Malbrain ML, Marik PE, Witters I, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. Anaesthesiology intensive therapy. 2014; 46(5):361–380. [PubMed: 25432556]
26. Maron BA, Hess E, Maddox TM, et al. Association of Borderline Pulmonary Hypertension With Mortality and Hospitalization in a Large Patient Cohort: Insights From the Veterans Affairs Clinical Assessment, Reporting, and Tracking Program. Circulation. 2016; 133(13):1240–1248. [PubMed: 26873944]
27. Adhikari NK, Burns KE, Friedrich JO, et al. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. Bmj. 2007; 334(7597):779. [PubMed: 17383982]
28. Afshari A, Brok J, Moller AM, et al. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults. The Cochrane database of systematic reviews. 2010; (7):CD002787. [PubMed: 20614430]
29. Gerlach H, Keh D, Semmerow A, et al. Dose-response characteristics during long-term inhalation of nitric oxide in patients with severe acute respiratory distress syndrome: a prospective, randomized, controlled study. American journal of respiratory and critical care medicine. 2003; 167(7):1008–1015. [PubMed: 12663340]
30. Benzing A, Mols G, Guttmann J, et al. Effect of different doses of inhaled nitric oxide on pulmonary capillary pressure and on longitudinal distribution of pulmonary vascular resistance in ARDS. British journal of anaesthesia. 1998; 80(4):440–446. [PubMed: 9640146]
31. Repesse X, Charron C, Vieillard-Baron A. Acute cor pulmonale in ARDS: rationale for protecting the right ventricle. Chest. 2015; 147(1):259–265. [PubMed: 25560864]

32. Repesse X, Charron C, Vieillard-Baron A. Acute respiratory distress syndrome: the heart side of the moon. Current opinion in critical care. 2015

33. Vieillard-Baron A, Price LC, Matthay MA. Acute cor pulmonale in ARDS. Intensive care medicine. 2013; 39(10):1836–1838. [PubMed: 23907498]

34. Vieillard-Baron A, Matthay M, Teboul JL, et al. Experts' opinion on management of hemodynamics in ARDS patients: focus on the effects of mechanical ventilation. Intensive care medicine. 2016

35. Bro-Jeppesen J, Hassager C, Wanscher M, et al. Targeted temperature management at 33 degrees C versus 36 degrees C and impact on systemic vascular resistance and myocardial function after out-of-hospital cardiac arrest: a sub-study of the Target Temperature Management Trial. Circulation Cardiovascular interventions. 2014; 7(5):663–672. [PubMed: 25270900]

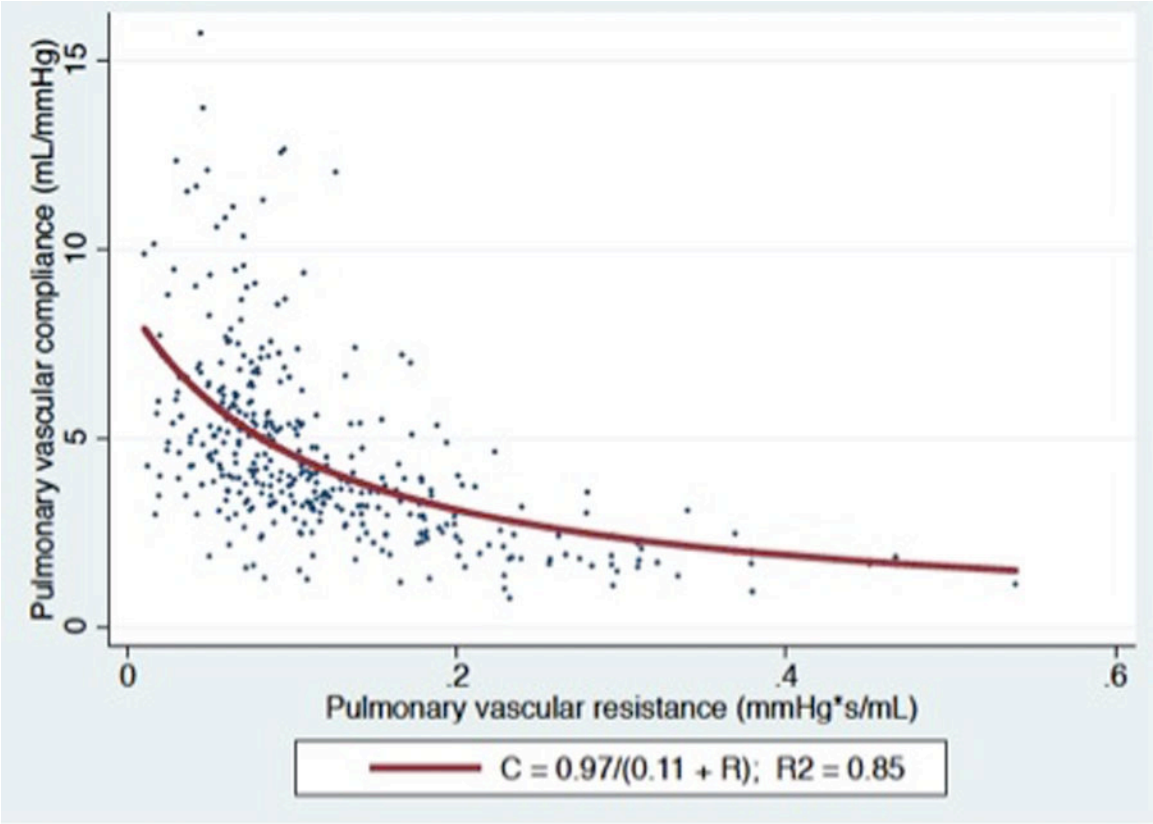
36. Wiener RS, Welch HG. Trends in the use of the pulmonary artery catheter in the United States, 1993-2004. Jama. 2007; 298(4):423–429. [PubMed: 17652296]

37. Friedberg MK, Feinstein JA, Rosenthal DN. Noninvasive assessment of pulmonary arterial capacitance by echocardiography. Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography. 2007; 20(2):186–190. [PubMed: 17275705]

38. Jozwiak M, Teboul JL, Anguel N, et al. Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. American journal of respiratory and critical care medicine. 2013; 188(12):1428–1433. [PubMed: 24102072]

39. Chemla D, Lau EM, Papelier Y, et al. Pulmonary vascular resistance and compliance relationship in pulmonary hypertension. The European respiratory journal. 2015

40. Tedford RJ. Determinants of right ventricular afterload (2013 Grover Conference series). Pulmonary circulation. 2014; 4(2):211–219. [PubMed: 25006440]



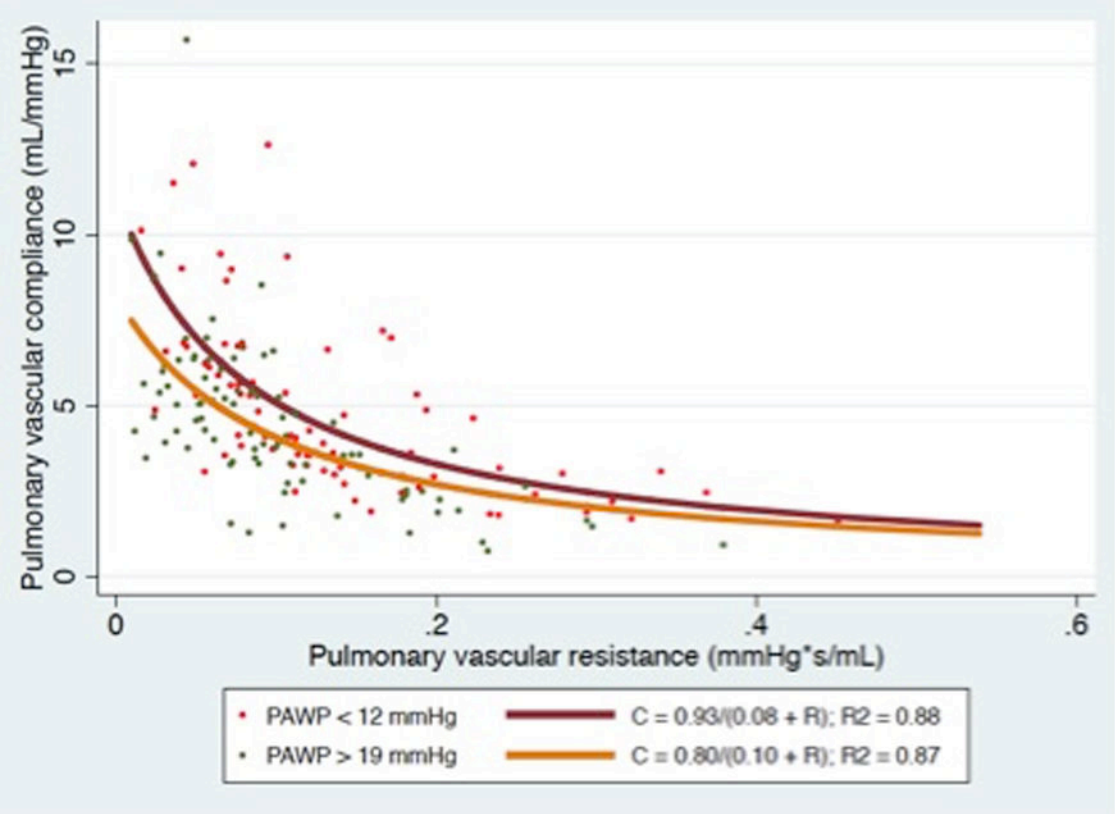
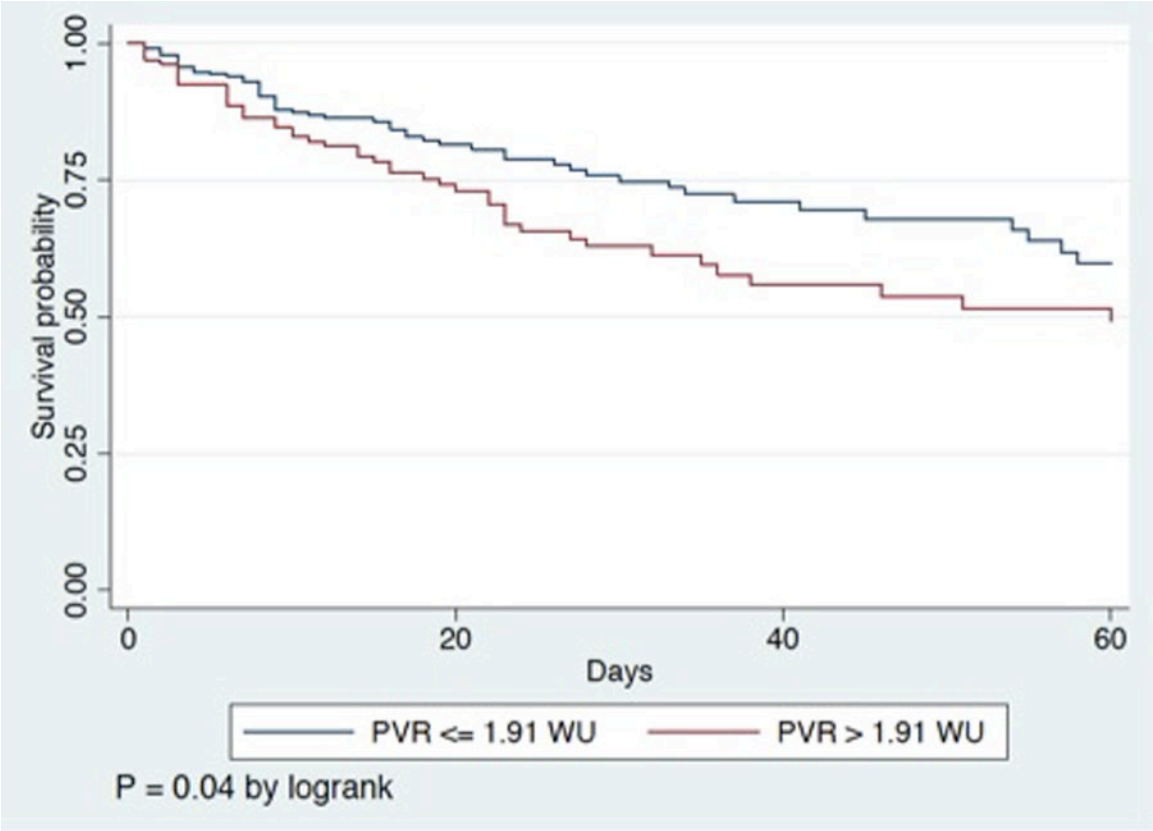


Figure 1.

Panel A) C_{PA} plotted as a function of PVR for the entire cohort. Panel B): C_{PA} as a function of PVR stratified by PAWP. ($P < 0.0001$ for comparison of curves after log-log transformation).



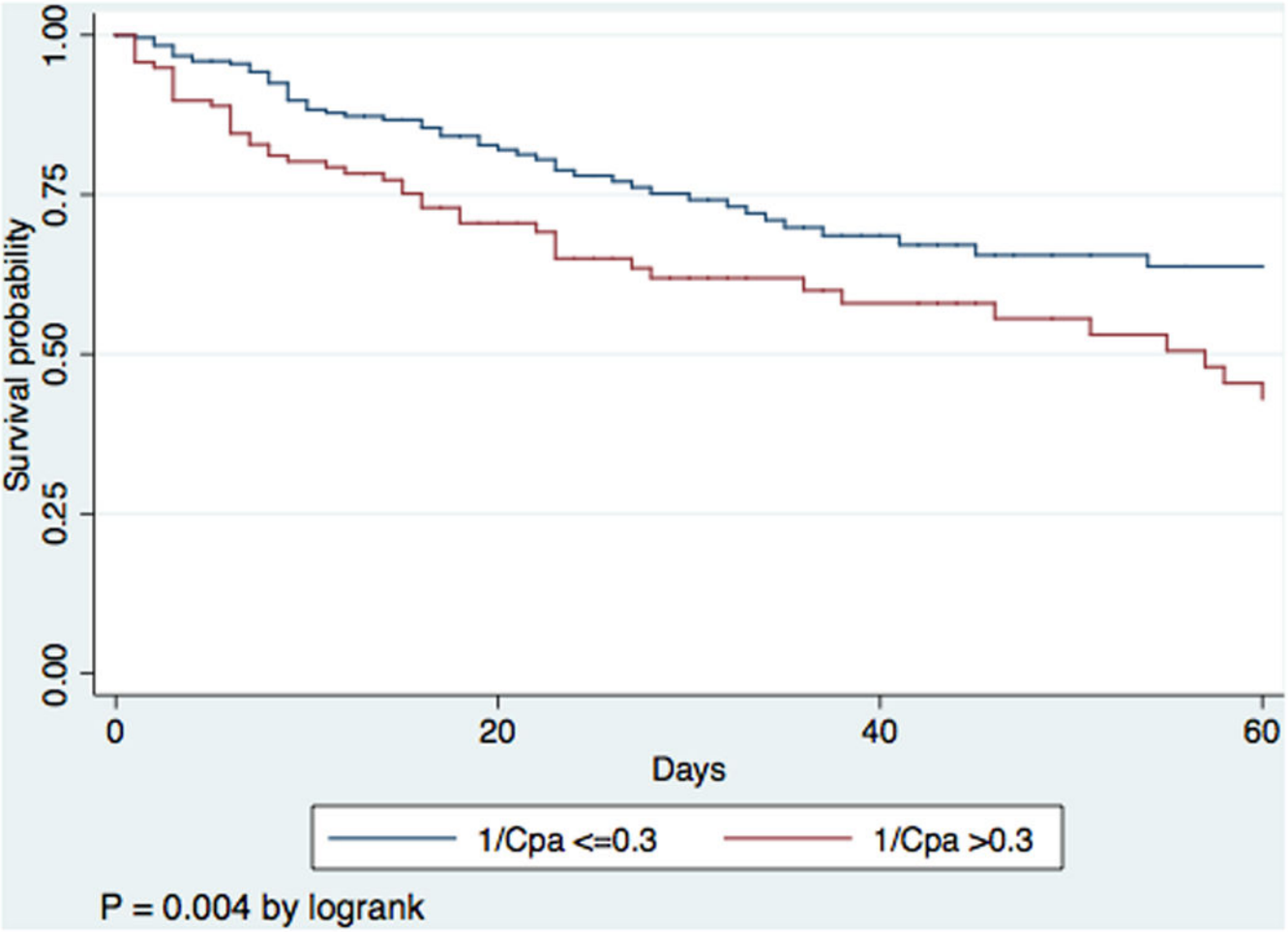
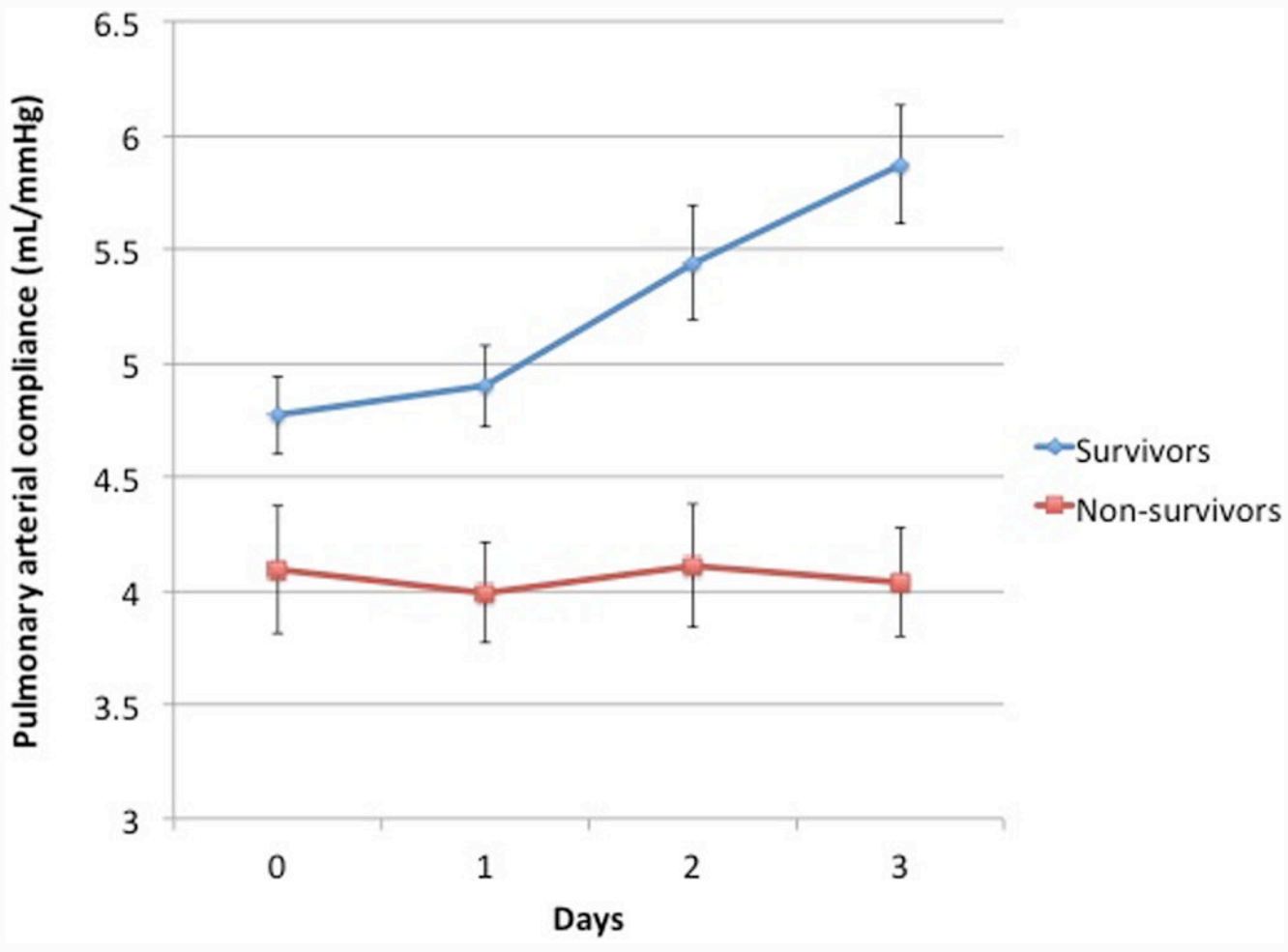


Figure 2.

Panel A) Kaplan-Meier survival curve for initial pulmonary vascular resistance (PVR) dichotomized by optimal cutpoint. Panel B) Kaplan-Meier survival curve for initial $1/C_{PA}$ dichotomized by optimal cutpoint



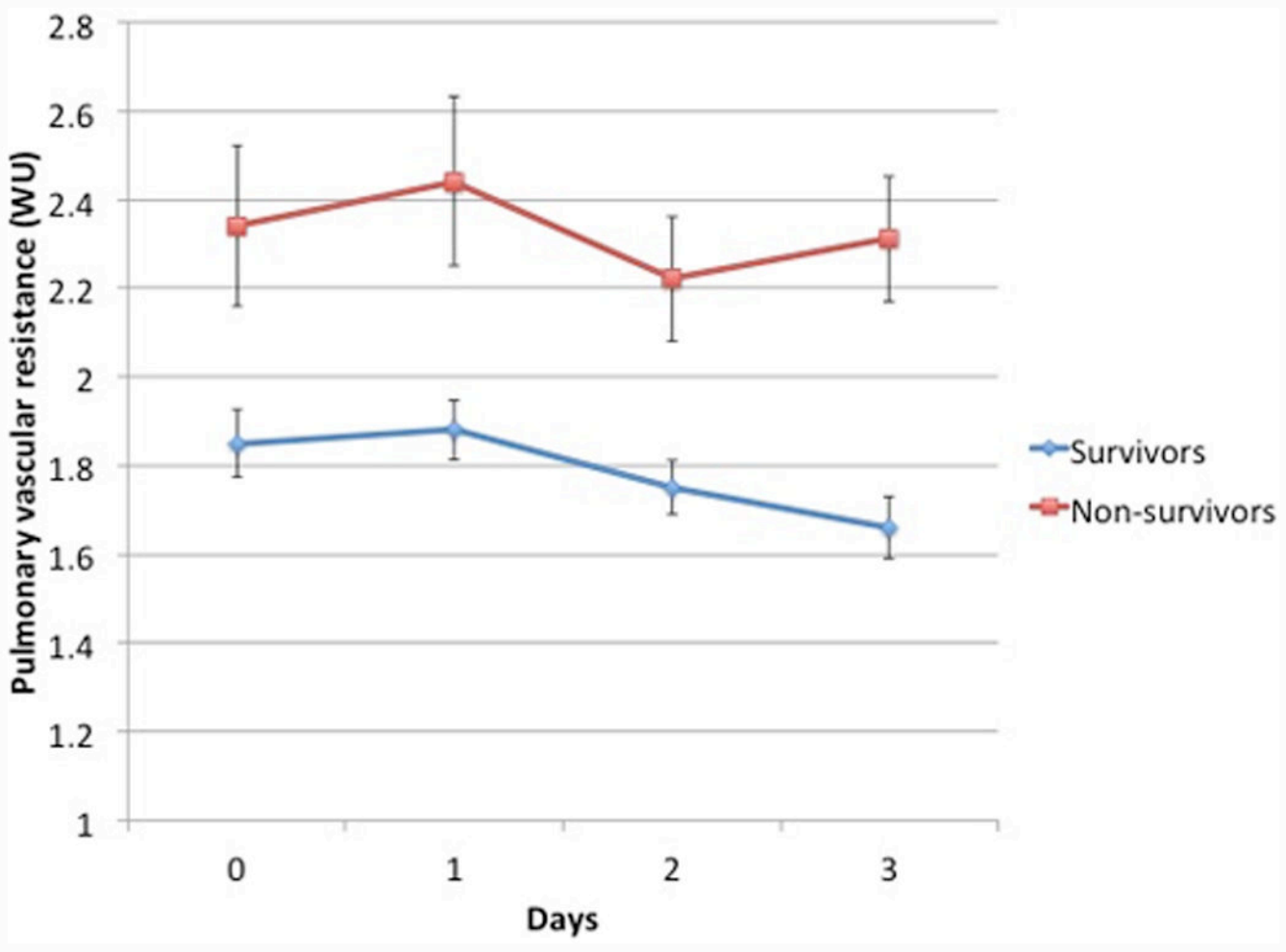


Figure 3.

Panel A) Mean C_{PA} on each of the first 4 trial days for subjects with available data at all 4 points who survived (N=209) versus those who died (N=71). C_{PA} did not change over time for non-survivors (P = 0.9 for trend) whereas it increased over time in survivors (P = 0.02 for trend).Panel B) Mean PVR on each of the first 4 trial days for subjects with available data at all 4 points who survived (N=194) versus those who died (N=68). PVR did not change in survivors (P = 0.1 for trend) or non-survivors (P = 0.6 for trend).

Table 1
Demographic, clinical and physiologic data, stratified by survival

Clinical factor	Overall (N=363)	Survived (N=261)	Died (N=102)	P
Age (years)	48 (38-61)	46 (37-58)	52 (41-67)	0.002
Male gender	190 (52%)	133 (51%)	57 (56%)	0.4
Caucasian race	238 (66%)	182 (70%)	56 (55%)	0.008
Body-surface area (m2)	1.9 (1.8-2.2)	2.0 (1.8-2.2)	1.9 (1.7-2.0)	0.003
Vasopressor use (%)	118 (33%)	73 (28%)	45 (44%)	0.003
Cause of ARDS (primary)				
trauma	27 (7%)	21 (8%)	6 (6%)	0.5
sepsis	78 (21%)	52 (20%)	26 (25%)	0.2
aspiration	52 (14%)	41 (16%)	11 (11%)	0.2
pneumonia	182 (50%)	129 (49%)	53 (52%)	0.7
other (ie, pancreatitis, fat embolism syndrome, near drowning, idiopathic)	21 (6%)	16 (6%)	5 (5%)	0.7
APACHE III score	93 (70-115)	86 (64-106)	109 (91-131)	0.00001
Tidal volume (mL)	450 (400-520)	450 (390-514)	450 (400-544)	0.4
PEEP (cm H2O)	10 (5-12)	10 (5-12)	8 (5-12)	0.9
Plateau pressure (cm H2O)	26 (22-30)	26 (22-30)	27 (22-31)	0.4
Driving pressure (cmH2O)	16 (13-20)	16 (13-20)	17 (13-23)	0.3
Peak pressure (cm H2O)	32 (27-38)	32 (26-37)	33 (27-39)	0.3
Fraction of inspired oxygen	0.6 (0.5-0.8)	0.6 (0.5-0.8)	0.6 (0.5-0.8)	0.3
Arterial pH	7.37 (7.3-7.43)	7.37 (7.31-7.43)	7.37 (7.28-7.42)	0.3
Arterial pCO2	39 (34-45)	40 (34-45)	39 (33-44)	0.4
A-a gradient	287 (200-411)	281 (191-406)	319 (210-434)	0.2
PaO2/fIO2 ratio	146 (100-200)	148 (102-200)	138 (88-202)	0.3
Arterial pO2	82 (68-103)	82 (68-103)	78 (66-104)	0.4

Data shown as median (IQR) or N(%). ARDS: acute respiratory distress syndrome; APACHE: acute physiology and chronic health evaluation; PEEP: positive end-expiratory pressure; A-a: alveolar-arterial

Table 2
Hemodynamic data, stratified by survival

Clinical factor	Overall (N=363)	Survived (N=261)	Died (N=102)	P
Systolic blood pressure (mmHg)	111 (97-129)	112 (100-130)	104 (94-117)	0.001
Diastolic blood pressure (mmHg)	59 (51-69)	60 (52-69)	55 (48-64)	0.002
Mean arterial pressure (mmHg)	76 (67-87)	79 (68-89)	71 (64-82)	0.0002
Heart rate (beats per minute)	100 (85-117)	98 (84-115)	106 (92-121)	0.02
Cardiac index (L/min/m2)	4.0 (3.2-5.1)	4.0 (3.3-5.1)	4.0 (3.0-5.0)	0.6
Stroke volume (mL)	80 (60-102)	83 (65-105)	72 (54-100)	0.007
Right atrial pressure (mmHg)	13 (9-16)	13 (10-17)	12 (8-14)	0.0007
PA systolic pressure (mmHg)	42 (36-50)	42 (36-49)	44 (36-51)	0.4
PA diastolic pressure (mmHg)	22 (18-27)	22 (18-27)	22 (18-27)	0.5
PA mean pressure (mmHg)	29 (24-35)	29 (24-35)	29 (24-35)	0.9
Pulmonary artery wedge pressure (mmHg)	16 (12-19)	16 (12-20)	15 (11-18)	0.02
Pulmonary vascular resistance (WU)	1.6 (1.1-2.5)	1.5 (1.0-2.4)	1.8 (1.1-3.0)	0.02
Pulmonary arterial compliance (mL/mmHg)	4.0 (3.0-5.6)	4.2 (3.2-6.0)	3.5 (2.6-5.3)	0.002
RC time (s)	0.41 (0.29-0.53)	0.41 (0.30-0.52)	0.40 (0.28-0.54)	0.8
Fluid balance (24 hours prior, mL)	196 (-16-498)	149 (-45-383)	296 (65-628)	0.0007
Temperature	37.5 (36.8-38.2)	37.6 (36.9-38.2)	37.4 (36.4-38.1)	0.05

Data shown as median (IQR) or N(%). PA: pulmonary artery; RC: resistance-compliance