Research Article

Pulmonary Circulation

Pulmonary and systemic hemodynamics are associated with myocardial injury in the acute respiratory distress syndrome

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Abstract

Background: Whether right and left heart hemodynamics are associated with myocardial injury in the acute respiratory distress syndrome (ARDS) is not known.

Methods: We performed a retrospective cohort study of subjects who had right heart catheterization within the ALVEOLI trial and Fluid and Catheter Treatment Trial. Myocardial injury was assessed using a highly sensitive troponin assay (hsTn; Abbot ARCHITECT). Hemodynamic variables included right atrial pressure, pulmonary artery wedge pressure, cardiac index and stroke volume, pulmonary vascular resistance, pulmonary arterial compliance, and pulmonary effective arterial elastance. We performed linear, logistic, and Cox regression to determine the association of hemodynamic variables with myocardial injury and to determine if hemodynamics mediated the association between myocardial injury and death.

Results: Among 252 ARDS patients, median day 0 troponin was 65.4 (13.8–397.8) ng/L. Lower cardiac index (β −0.23 SE 0.10; $P < 0.001$) and stroke volume (β −0.26 SE 0.005; $P < 0.001$), higher pulmonary vascular resistance (β 0.22 SE 0.11; $P < 0.001$), lower pulmonary arterial compliance (β −0.24 SE 0.06; $P < 0.001$), and higher arterial elastance (β 0.27 SE 0.43; $P < 0.001$) were associated with greater myocardial injury in univariable and adjusted models. Changes in stroke volume, cardiac index, pulmonary arterial compliance, pulmonary vascular resistance, and arterial elastance were all associated with progressive myocardial injury over three days. hsTn levels were associated with mortality; however, the association was attenuated after adjustment for each of stroke volume, pulmonary vascular resistance, pulmonary arterial compliance, and arterial elastance.

Conclusion: Pulmonary vascular hemodynamics are associated with myocardial injury in ARDS, while filling pressures are not. Pulmonary vascular disease may represent a treatable contributor to myocardial injury in ARDS.

Keywords

acute respiratory distress syndromes (ARDS) and acute lung injury, cardiac output, hemodynamics, pulmonary artery, pulmonary circulation

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Introduction

The acute respiratory distress syndrome (ARDS) is a common cause of respiratory failure[1] with persistently high mortality rates and responsible for substantial morbidity in the short and long term.[1–3] Novel diagnostic and therapeutic paradigms are needed to improve patient outcome.[4,5] Investigators have recently identified right heart failure and pulmonary vascular dysfunction as important prognostic factors in ARDS,[6–12] and there is increasing interest in treatment approaches to protect the right ventricle in ARDS.[10,13–15] Left heart function is also prognostic

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in critically ill patients[16]; thus, cardiovascular hemodynamics and pulmonary and systemic vascular function represent useful and novel diagnostic, prognostic, and therapeutic factors in ARDS patients. The mechanism of the association of cardiovascular hemodynamics with outcome in ARDS is not defined – one possible mechanism could be increased right and left heart strain leading to myocardial injury manifested by increased circulating troponin. Myocardial injury is common in ARDS and associated with adverse outcome.[17,18] Whether right and left heart hemodynamics are associated with myocardial injury is not known; optimizing hemodynamics could represent a treatable manifestation of critical illness to reduce myocardial injury and possibly improve ARDS outcome. To address these knowledge gaps including the unknown relationships between myocardial injury, hemodynamics, and outcome in ARDS, we performed a multi-center retrospective cohort study of patients with ARDS with pulmonary artery catheters in place to determine the association of right and left heart hemodynamics with myocardial injury assessed with high sensitivity troponin-I (hsTnI), the association of trend in hemodynamics with progressive myocardial injury and whether adjusting for hemodynamics attenuates the association of myocardial injury with outcome. We hypothesized that pulmonary vascular hemodynamics would be associated with myocardial injury and that hemodynamics may mediate the relationship between myocardial injury and outcome in ARDS.

Methods

Patient population

The study cohort included 252 patients from two previously completed clinical trials in ARDS. The ALVEOLI trial randomized 549 patients with ARDS from 23 centers to a higher versus lower level of positive end-expiratory pressure.[19] The Fluid and Catheter Treatment Trial (FACTT) randomized 1000 patients with ARDS from 20 intensive care units (ICUs) to placement of a central venous catheter or pulmonary artery catheter and to a liberal or conservative fluid management strategy.[20,21] Inclusion criteria for these trials was similar and included patients with partial pressure of oxygen to fraction of inspired oxygen ratio below 300, acute onset of pulmonary infiltrates, and no suspicion for elevated left atrial pressure or cardiogenic pulmonary edema. Relevant exclusion criteria included acute myocardial infarction and chronic lung and neuromuscular disease. Very few patients in FACTT (27 of 1000) had a history of chronic heart failure, and the ALVEOLI trial did not report data on chronic heart failure. We obtained data and plasma from both trials via the NIH Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC).[22] The cohort for this study included all 252 patients from both trials who were intubated within 24 h of study entry, who had available plasma on study day 0, and who had complete hemodynamic and clinical data available on trial day 0 including right atrial and pulmonary artery pressure, pulmonary artery wedge pressure (PAWP), and cardiac index (CI) as well as height and weight to calculate cardiac output and stroke volume (SV). A comparison of clinical and demographic data for the cohort studied herein who had pulmonary artery catheterization compared to parent study is shown in the Supplemental Table. Included and excluded patients had similar age, race, sex, Sequential Organ Failure Assessment (SOFA) score and PaO_2/FiO_2 ratio. Excluded patients had slightly lower heart rates and slightly higher rates of vasopressor use. Rates of death and number of ICU free days and ventilator free days were similar between patients included in this analysis and those excluded.

Participants in both trials gave informed consent, and the participating institutional review boards (IRB) gave their approval.[19–21] For the present study, the Johns Hopkins IRB approved the study which is a secondary analysis of data, and specimens available on request from the BioLINCC and were de-identified, containing no protected health information.

Laboratory methods

We measured hsTnI from EDTA anticoagulated plasma using Abbott Laboratories' ARCHITECT STAT assay. The limit of detection for this assay was 2 ng/L. For subjects with hsTnI below this value, the value was set at 1.3 ng/L (2 ng/L divided by $\sqrt{2}$) for analysis. Upper limit of normal, corresponding to the 99th percentile value of a healthy reference population, was 26 ng/L.[23]

Study outcomes and covariates

The goal of our study was to determine hemodynamic factors associated with myocardial injury. The primary endpoint was hsTn concentration. Relevant covariates included right and left heart filling pressure assessed by right atrial pressure (RAP) and PAWP, respectively, CI and SV, pulmonary vascular resistance (PVR) and pulmonary arterial compliance (PAC), systemic vascular resistance (SVR) and systemic arterial compliance (SAC), and pulmonary effective arterial elastance (Ea) and systemic effective arterial elastance (sysEa). Hemodynamics including filling pressures and SV and cardiac output were measured by study investigators at the point of care per guidelines from the clinical trial protocols. PVR was calculated as (mean PA pressure−PAWP)/CO, while SVR was calculated as (mean arterial pressure–RAP)/CO. PAC was calculated as SV/PA pulse pressure,[24] while SAC was calculated as SV/systemic pulse pressure. Ea was calculated as PA systolic pressure/SV if mean PA pressure was greater than 25 mmHg and PA mean pressure/SV if mean PA pressure was less than 25.[25–28] sysEa was calculated as 0.9×systolic blood pressure/SV. A subset of 109 patients with available

hemodynamic and biochemical data on trial day 3 was analyzed based on the trend in hsTnI between day 0 and day 3. Patients with hsTnI increasing more than 20% between day 0 and day 3 were considered to have progressive myocardial injury. We performed logistic regression to determine the association of change in hemodynamics with progressive myocardial injury. For a final set of analyses, we determined the association of exposure variable myocardial injury with outcome variable of in-hospital 60-day mortality adjusting for hemodynamics to determine whether the association of myocardial injury and outcome was dependent or independent of hemodynamics.

Statistical analysis

The dependent outcome variable was hsTnI concentration. hsTn was non-normal by Shapiro-Wilk test and was log-transformed. Hemodynamic variables were considered as independent variables, and univariable and multivariable linear regressions were performed to identify which hemodynamic parameters were associated with myocardial injury. Multivariable models were adjusted for factors of a priori clinical interest including patient age, sex, and SOFA score on day 0.[29] The assumptions of linear regression were verified by inspection of the residuals versus predicted values plot and inspection of the residuals for normal distribution using Q–Q plots We performed univariable and adjusted logistic regressions to assess the association of change in hemodynamics with progressive myocardial injury again adjusting for age, sex, and SOFA score determined a priori as a surrogate for severity of critical illness. Finally, we performed Cox Proportional Hazard models of the association of exposure hsTn level with outcome of 60-day in-hospital mortality adjusting for each hemodynamic parameter to determine whether the inclusion of hemodynamics attenuated the relationship between myocardial injury and outcome in ARDS. A two-tailed p-value of less than 0.05 was considered statistically significant. Data were analyzed with Stata version 14.0 (StataCorp Inc., College Station, TX).

Results

Patient demographics and clinical characteristics are shown in Table 1. Median age of 252 eligible ARDS patients was 49 (39–62) years, median SOFA score 9 (6–11), and 37.7% received vasopressors. Median day 0 troponin was 65.4 (13.8–397.8) ng/L, and 95.6% of patients had detectable circulating troponin and 29% of the group died within 60 days.

Hemodynamic data are shown in Table 2. Median right and left heart filling pressures were elevated, with RAP 12 mmHg (interquartile range (IQR) 10–15 mmHg) and PAWP 15 mmHg (IQR 12–18 mmHg). Median CI was elevated to 3.7 L/min/m^2 (IQR 3.04–4.7 L/min/m^2) consistent with hyperdynamic circulatory state. Models assessing the association of hemodynamic parameters with myocardial injury are shown in Tables 3 and 4. Right and left heart filling pressures – assessed via RAP or central venous pressure and PAWP – were not associated with hsTn, whereas

Table 1. Demographics and clinical characteristics for 252 ARDS patients.

Age (yr)	49 (39–62)
Male sex, n (%)	134 (53.2)
Caucasian race, n (%)	165 (65.5)
Body surface area (m^2)	1.9 (1.7–2.1)
Tidal volume (mL)	490 (400–558)
Positive end-expiratory pressure (cm H_2O)	10 (5–12)
Plateau pressure (cm H_2O)	27 (22–31)
Fraction of inspired oxygen	0.6 (0.5–0.88)
Arterial pH	7.37 (7.3–7.44)
Arterial pCO_2 (mmHg)	39 (33–44)
PaO_2/fiO_2 ratio	138 (93–186)
Arterial PO_2 (mmHg)	81 (68–105)
Temperature (°C)	37.6 (37.0–38.2)
Heart rate (bpm)	105 (90–120)
Troponin	65.4 (13.8–397.8)
Vasopressor use, n (%)	95 (38)
Height (cm)	170 (163–178)
Weight (kg)	80 (68–94)
Creatinine, mg/dL	1.2 (0.8–2.0)
Cumulative fluid balance over 3 days (L)	3.1 (−0.6 to 8.6)
Death, n (%)	73 (29)
ICU free days within first 30 days (days)	14 (0–21)
Ventilator free days within first 30 days (days)	17 (0–22)

Note: Data are shown as median (interquartile range) and N (%). PaO_2: partial pressure of oxygen; fiO_2: fraction of inspired oxygen; pCO_2: partial pressure of CO_2.

Table 2. Systemic and pulmonary vascular hemodynamics for 252 ARDS patients.

Systolic BP (mmHg)	109 (97–124)
Diastolic BP (mmHg)	59 (51–66)
Mean arterial pressure (mmHg)	75 (68–86)
Right atrial pressure (mmHg)	12 (10–15)
Pulmonary artery wedge pressure (mmHg)	15 (12–18)
Cardiac index (L/min/m^2)	3.7 (3.04–4.7)
Stroke volume (mL)	71 (56–92)
Pulmonary artery systolic pressure (mmHg)	41 (35–49)
Pulmonary artery diastolic pressure (mmHg)	22 (18–27)
Pulmonary vascular resistance (WU)	1.8 (1.2–2.7)
Pulmonary arterial compliance (mL/mmHg)	3.9 (2.8–5.6)
Systemic vascular resistance (WU)	8.9 (6.7–11.4)
Systemic arterial compliance (mL/mmHg)	1.4 (1.0–1.9)
Pulmonary effective arterial elastance (mmHg/mL)	0.53 (0.37–0.74)
Systemic effective arterial elastance (mmHg/mL)	1.4 (1.1–1.9)

Note: Data are shown as median (interquartile range).

Table 3. Correlations of myocardial injury with hemodynamic measurements; shown are univariable and adjusted linear regressions with hemodynamic parameters as independent variables and hsTn as the dependent variable.

	Univariable models β (SE)	P	Adjusted for age, sex, SOFA score β (SE)	P
Right atrial pressure (mmHg)	0.024 (0.033)	0.7	0.032 (0.034)	0.62
Pulmonary artery wedge pressure (mmHg)	0.033 (0.030)	0.6	0.045 (0.03)	0.48
Cardiac index (L/min/m^2)	−0.23 (0.1)	0.001	−0.27 (0.11)	0.001
Stroke volume (mL)	−0.26 (0.0048)	0.001	−0.25 (0.0048)	0.001
Pulmonary vascular resistance (WU)	0.22 (0.11)	0.001	0.22 (0.11)	0.001
Pulmonary arterial compliance (mL/mmHg)	−0.23 (0.065)	0.001	−0.21 (0.069)	0.001
Systemic vascular resistance (WU)	0.20 (0.035)	0.002	0.23 (0.037)	0.001
Systemic arterial compliance (mL/mmHg)	−0.22 (0.19)	0.001	−0.23 (0.19)	0.001
Pulmonary effective arterial elastance (mmHg/mL)	0.27 (0.43)	0.001	0.25 (0.44)	0.001
Systemic effective arterial elastance (mmHg/mL)	0.26 (0.23)	0.001	0.25 (0.23)	0.001

SE: standard error.

Table 4. Association of changes in hemodynamic parameters with rising troponin (20% or greater increase) between day 0 and day 3, for 109 patients with available data.

	Univariable models OR (95% CI)	P	Adjusted for age, sex, SOFA score OR (95% CI)	P
Cardiac index (L/min/m^2)	0.41 (0.22–0.75)	0.004	0.35 (0.18–0.67)	0.002
Stroke volume (mL)	0.28 (0.13–0.57)	0.001	0.26 (0.12–0.54)	0.001
Pulmonary vascular resistance (WU)	1.65 (1.01–2.68)	0.044	1.72 (1.036–2.86)	0.036
Pulmonary arterial compliance (mL/mmHg)	0.57 (0.35–0.91)	0.019	0.54 (0.33–0.88)	0.014
Systemic vascular resistance (WU)	1.88 (1.16–3.04)	0.01	1.90 (1.16–3.09)	0.01
Systemic vascular compliance (mL/mmHg)	0.59 (0.37–0.93)	0.023	0.57 (0.36–0.91)	0.018
Pulmonary effective arterial elastance (mmHg/mL)	1.98 (0.15–3.39)	0.014	2.01 (1.15–3.51)	0.015
Systemic effective arterial elastance (mmHg/mL)	4.23 (2.05–8.75)	0.001	4.25 (2.04–8.86)	<0.001

SOFA: Sequential Organ Failure Assessment; OR: odds ratio; CI: confidence interval.

cardiac output and SV were both associated with hsTn in univariable and adjusted models (Fig. 1). Increasing PVR and decreasing PAC were associated with larger amounts of myocardial injury (Fig. 2). Likewise, increasing SVR and decreasing SAC were also associated with larger amounts of myocardial injury (Fig. 2). Pulmonary and systemic effective Ea were both associated with myocardial injury (Fig. 3).

Of 109 subjects with plasma on day 0 and 3, 27.5% had progressive myocardial injury. After adjusting for age, sex, and SOFA score, increasing CI and SV and increasing PAC and SAC were associated with lower odds of progressive myocardial injury (Table 4). Conversely, increasing PVR and SVR and increasing pulmonary and systemic Ea were associated with greater odds of progressive myocardial injury (Tables 3 and 4).

As shown in Table 5, hsTn level was associated with mortality in univariable survival analysis. The association was partially attenuated in magnitude after concurrent adjustment by each of: SV, PVR, PAC, and Ea. Concurrent adjustment by each of CI, SAC, SVR, and sysEa had less impact on the association of myocardial injury with outcome. In no cases did the hazard ratio approach 1.0 with adjustment.

Discussion

In this multi-center cohort study of patients with ARDS with pulmonary artery catheters in place, we investigated the association of hemodynamic parameters with myocardial injury. First, we report that right and left heart filling pressure – assessed by RAP and PAWP – is not associated with myocardial injury, whereas cardiac output and SV, and PVR and SVR and compliance and pulmonary and systemic Ea were independently associated with myocardial injury. Second, changes in these hemodynamic parameters were all associated with progressive myocardial injury over three days. Third, pulmonary vascular hemodynamics partially attenuate the magnitude of the relationship between

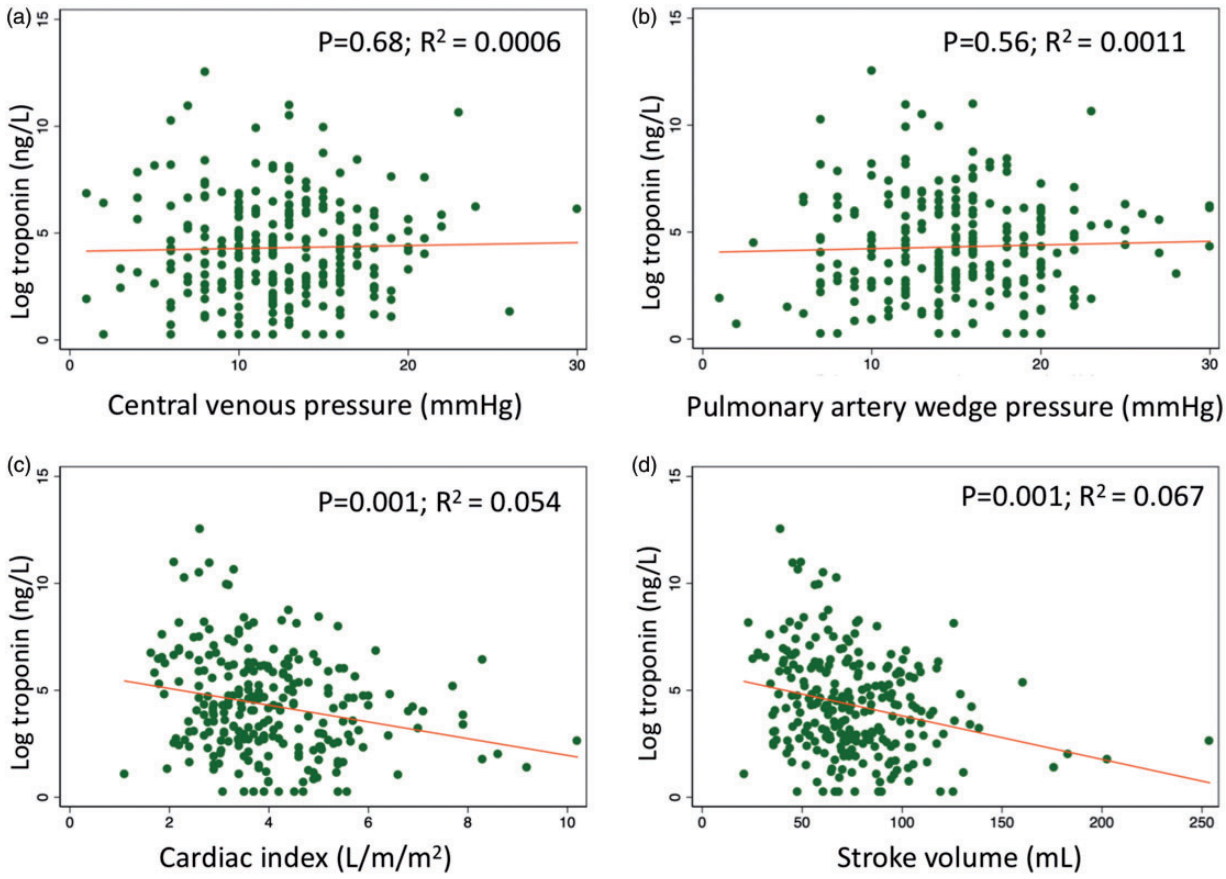

Fig. 1. Association of filling pressures and cardiac index and stroke volume with myocardial injury. Panel A: central venous pressure and troponin; panel B pulmonary artery wedge pressure and troponin; panel C: cardiac index and troponin and panel D: stroke volume and troponin.

myocardial injury and outcome in ARDS to a greater extent than systemic hemodynamics suggesting a conceptual hypothetical model that targeting pulmonary vascular hemodynamics could contribute in part to reducing myocardial injury and improve ARDS outcome.

Myocardial injury in ARDS and hemodynamic mechanisms

Prior work by our group identified that myocardial injury – manifested by elevated levels of hsTn – is present in over 90% of ARDS patients and is associated with mortality as a function of underlying critical illness,[17] and other groups have also reported that myocardial injury is associated with ARDS outcome.[30,31] The mechanism of this association is not clear; we reported factors reflecting underlying critical illness were associated with hsTn levels, including creatinine, SOFA score, and heart rate.[17] Rivara et al. report that ARDS patients with myocardial injury manifested more tricuspid regurgitation and regional wall motion abnormalities.[31] Our present study adds to this evidence base by establishing that markers of increased right and left heart afterload and indices of forward flow – namely SV and cardiac output – are associated with myocardial injury. Causality cannot be inferred on the basis of this observational study; however, a conceptual hypothesis could be that ARDS causes pulmonary parenchymal disease, hypoxemia and alveolar flooding leading to increased right ventricular afterload, myocardial injury, and reduced cardiac function. Analogously, increased left ventricular afterload could induce myocardial injury and reduced cardiac function by a similar mechanism.

Right heart and myocardial injury

Right ventricular afterload itself has been associated with outcome in ARDS – Bull et al. reported that the PVR was associated with mortality in the FACTT cohort,[7] and our group reported both PVR and PAC were associated with outcome.[12] Conceptually, PVR represents the static right ventricular afterload, whereas PAC represents the pulsatile RV afterload.[32] Our present work suggests a hypothetical mechanism whereby these markers of RV afterload could mitigate adverse outcome – that increased RV afterload leads to more myocardial injury. Prior work identified clinical factors associated with PVR such as lower body temperature and higher ventilator driving pressure and clinical factors associated

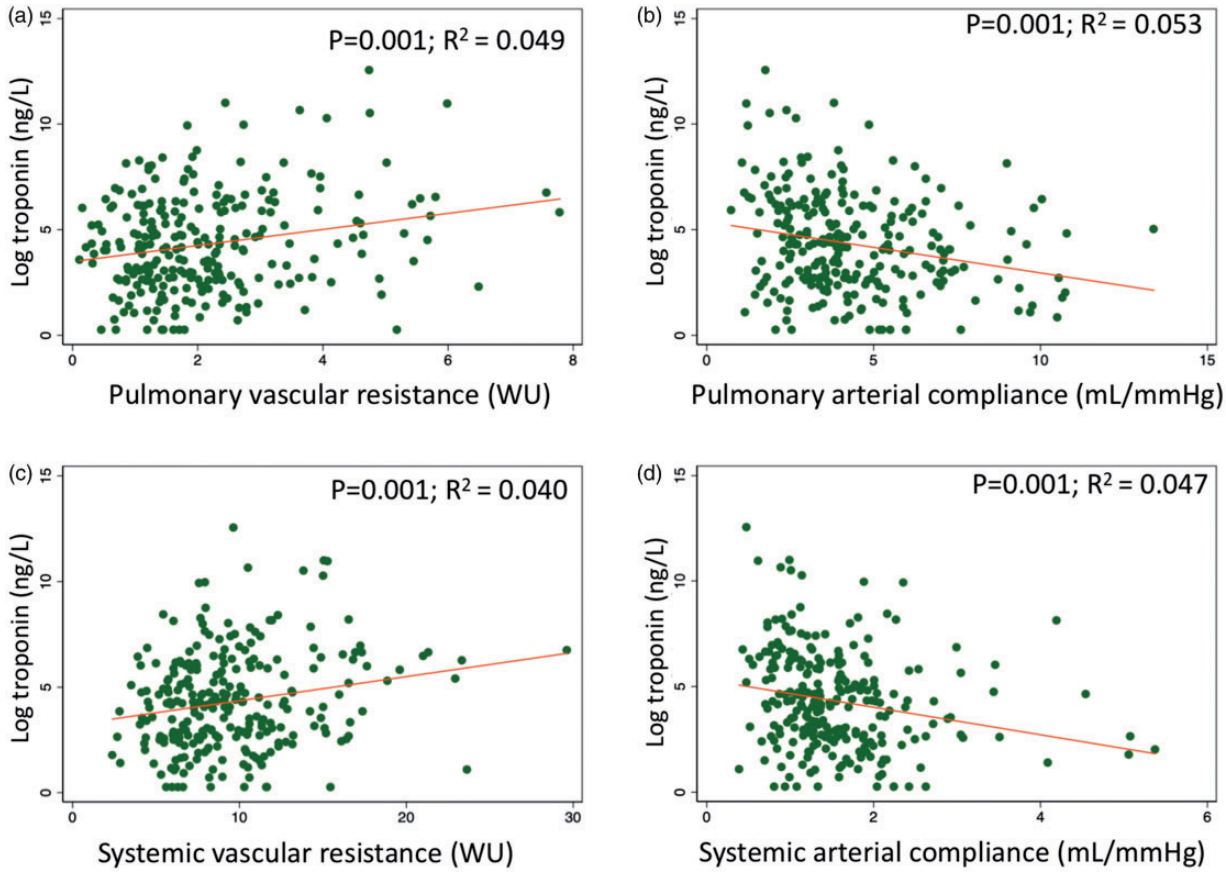

Fig. 2. Association of pulmonary and systemic vascular resistance and compliance with myocardial injury. Panel A: pulmonary vascular resistance and troponin; panel B: pulmonary arterial compliance and troponin; panel C: systemic vascular resistance and troponin; panel D: systemic arterial compliance and troponin.

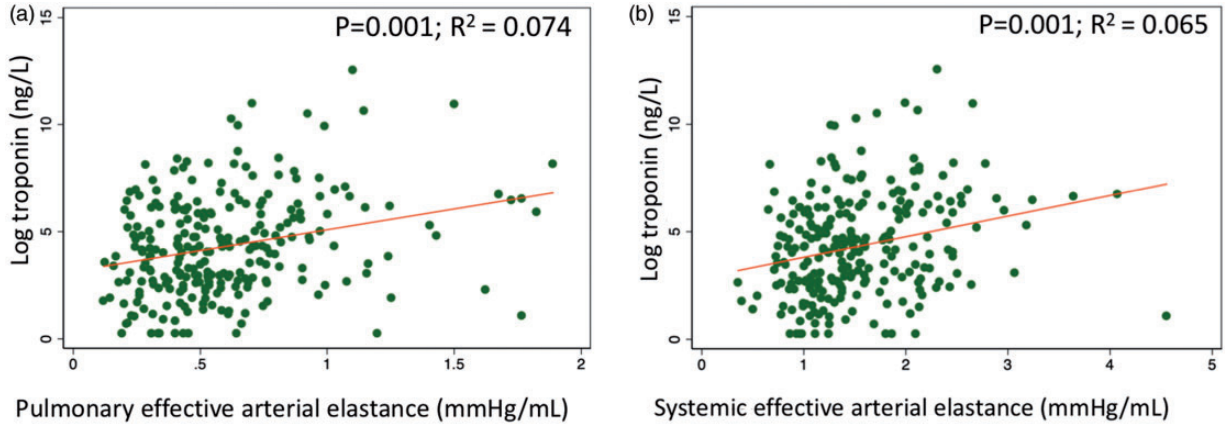

Fig. 3. Association of pulmonary and systemic effective arterial elastance with myocardial injury. Panel A: pulmonary effective arterial elastance and troponin; Panel B: systemic effective arterial elastance and troponin.

with PAC included lower arterial pH and positive fluid balance.[12] Body temperature and pH were also associated with myocardial injury.[17] Whether targeting RV afterload therapeutically with fluid restriction, minimizing driving pressure, minimizing acidosis, and following RV function with hemodynamics or echocardiography using an "RV protective" strategy[13–15,33] would reduce myocardial injury is not known but should be explored in a prospective fashion.

Systemic circulation and myocardial injury

We report that the SVR and the SAC are associated with myocardial injury. Unlike in the pulmonary circulation

Table 5. Association of myocardial injury with mortality adjusting for hemodynamic factors.

	Hazard ratio per IQR of day 0 troponin (95% CI)	P
Unadjusted	1.0032 (1.00038–1.0060)	0.026
Stroke volume	1.0026 (0.9996–1.0056)	0.085
Cardiac index	1.0030 (1.000072–1.0060)	0.045
Systemic arterial compliance	1.0029 (1.000032–1.0058)	0.047
Systemic vascular resistance	1.0032 (1.00034–1.0060)	0.029
Pulmonary arterial compliance	1.0026 (0.9996–1.0056)	0.089
Pulmonary vascular resistance	1.0025 (0.9994–1.0055)	0.11
Pulmonary effective arterial elastance	1.0027 (0.9998–1.0056)	0.072
Systemic effective arterial elastance	1.0030 (1.00005–1.006)	0.046

IQR: interquartile range; CI: confidence interval.

where the PVR and PAC are likely distributed over the same anatomic compartment, in the systemic circulation the muscular proximal aorta comprises most of the compliance portion of the circuit whereby the resistance component of the circuit resides in the smaller arterioles.[24] We report that both pulsatile and resistive afterload is associated with myocardial injury. Arterial compliance has been associated with outcome in other settings including primary cardiac prevention[34,35] and results in increased LV afterload and reduced left ventricular (LV) function.[36] Thus, reduced arterial compliance, which localizes to the proximal aorta and branch vessels, could represent a surrogate for nascent cardiovascular risk factors predisposing to myocardial injury and adverse hemodynamic consequences. The SVR is often pharmacologically manipulated in managing critical illness through the use of vasoactive drugs. Whether targeting a specific SVR via choice of vasopressors to reduce myocardial injury is not known. Reduced arterial compliance and increased resistance were also associated with higher LV diastolic stiffness,[37] which could synergistically cause more diastolic dysfunction and adverse hemodynamic consequences leading to myocardial injury during critical illness.

Progressive myocardial injury

We report that changes in these hemodynamic parameters over time are likewise associated with greater or lower odds of progressive myocardial injury. Given that progressive myocardial injury is independently associated with ARDS outcome,[18] understanding the pathophysiology of progressive myocardial injury and potential treatment targets could improve outcome. Our finding that pulmonary hemodynamics attenuate the relationship between myocardial injury and outcome suggests that targeting pulmonary vascular hemodynamics should be further studied.

Limitations

Limitations of our study include its retrospective, observational design. As such, causality is not implied and our findings represent hypothesis generating associations. An analytic limitation is that the optimal approach for formal mediation analysis of survival data is not clear.[38] Hemodynamic data were only collected for a subset of patients in FACTT and ALVEOLI and as such, our analysis reflects only a subset of the entire study cohorts. Similarly, the FACTT and ALVEOLI datasets do not include data assessing structural cardiac abnormalities, such as echocardiography, nor detailed medical therapy for cardiovascular disease, such as aspirin therapy, statin therapy, or anticoagulants.

Troponin measurements were only available on day 0 and day 3 time points, and ECG and cardiac imaging data were not obtained; thus, strict adjudication as to whether the elevation in hsTn represents myocardial infarction versus myocardial injury is not possible. However, both trials excluded patients with clinical cardiac ischemia and enrolled very few patients with heart failure or structural heart disease[19–21]; therefore, it is unlikely that patients with clinical acute MI are included in our cohort. Finally, this assessment relies on invasive hemodynamics, and fewer patients are assessed with right heart catheterization in the context of ARDS.[39] Pulmonary hemodynamics can be determined using echocardiography,[40] and targeting echo-based hemodynamics should be investigated in prospective trials. Not all patients in the parent trials underwent right heart catheterization and it is likely that patients undergoing right heart catheterization have a different clinical profile than those that did, which impacts generalizability. However, comparison of included and excluded patients shows overall comparable demographics, clinical outcomes, and degree of critical illness (Supplemental Table).

In conclusion, we report that hemodynamic markers of pulmonary and systemic afterload are associated with myocardial injury in ARDS. Pulmonary vascular disease may be involved in the relationship between myocardial injury and outcome in ARDS and further mechanistic and therapeutic studies are warranted. Whether targeted therapy to improve hemodynamics could mitigate myocardial injury in ARDS should be assessed in future trials and could represent a strategy to improve ARDS outcome.

Conflict of interest

The reagents and assays for this study were provided from Abbott Laboratories via an unrestricted investigator initiated grant; Abbott had no role in the study design, manuscript preparation, or decision to submit the manuscript for publication. Metkus performs consulting unrelated to this subject matter for BestDoctors Inc. and Oakstone/EBIX. Metkus received royalties for a textbook publication for McGraw-Hill Publishing, unrelated to this subject matter.

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Supplemental Material

Supplemental material for this article is available online.

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