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Graded response of the pulmonary circulation to progressive pulmonary embolism in sheep: From compensation to lethal right heart failure

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BACKGROUND: Severe pulmonary embolism (PE) with right heart failure (RHF) has high mortality. To more fully understand PE progression, we evaluated the right ventricle (RV) and pulmonary circulation response to graded PE in an acute PE sheep model.

METHODS: Polydextran beads were intravenously administered every 15 minutes in 250 mg doses to adult female sheep (n = 8) until death. Concurrent pulmonary artery (PA) blood flow/pressure was measured. RV pressure-volume (P-V) loops were generated with a conductance catheter. Pulmonary vascular resistance was used to stage PE severity into mild, moderate, and severe groups.

RESULTS: All sheep developed graded RHF. For mild, moderate, and severe PE, 3, 6, and 9 doses were needed, respectively. Only 1 additional dose triggered death. In severe PE, mean PA pressure reached 42 ± 6 mm Hg with significantly decreased cardiac output (CO). Pulmonary impedance spectra showed significantly increased Z_0 (RV static load) and Z_1 (RV pulsatile load). PE shifted the RV P-V loop from lower left triangular to upper right rectangular shape. PA elastance (Ea, RV afterload) and end-systolic elastance (Ees, RV contractility) progressively increased. Ees/Ea (RV-PA coupling) was initially maintained but became uncoupled in severe PE, causing RHF.

CONCLUSIONS: Compensatory increases in RV contractility initially maintain CO in PE despite RV afterload elevation. Increased RV contractility eventually fails to compensate for elevated RV

Abbreviations: ABP, arterial blood pressure; CO, cardiac output; CVP, central venous pressure; Ea, pulmonary artery elastance; EDP, end-diastolic pressure; EDV, end-diastolic volume; Ees, end-systolic elastance; EF, ejection fraction; ESP, end-systolic pressure; ESPVR, end-systolic pressure-volume relation; ESV, end-systolic volume; LAP, left atrial pressure; PA, pulmonary artery; PAP, pulmonary artery pressure; PE, pulmonary embolism; PV, pressure volume; PVR, pulmonary vascular resistance; RHF, right heart failure; RV, right ventricle; RVEF, right ventricle ejection fraction; SV, stroke volume; SW, stroke work

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afterload, causing RV-PA uncoupling in severe PE with RHF. Severe PE rapidly progresses to lethal RHF and will likely require immediate intervention to prevent death.
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Background

Acute pulmonary embolism (PE), which is the sudden blockage of the pulmonary artery (PA), has an annual incidence of 100 to 200 per 100,000 person-years.[1-3] PE is the third most common cause of cardiovascular mortality. Additionally, PE has a 20% mortality at 6 months, and 100,000 PE deaths occur annually in the United States.[4-6]

Normally, the lungs act as a bio-filter to capture venous thrombi/other emboli and prevent them from entering the systemic circulation, mitigating major organ embolization and subsequent infarction or stroke.

However, PE can occur when the amount of PA emboli exceeds the lung filtering capacity. This leads to increased pulmonary vascular resistance (PVR) and subsequent PA pressure (PAP) elevation, resulting in right ventricle (RV) strain with increased potential for right heart failure (RHF).[7,8] RV functional status is a critical determinant of PE patient outcomes, and RHF significantly increases PE mortality.[5,7,8] The majority of PE patients are slightly symptomatic or asymptomatic with no sign of RV compromise and are low risk with < 1% mortality.[9] PE patients with RV dysfunction and/or elevated biomarkers are classified as submassive PE with intermediate risk and 6% to 8% mortality.[10] RV dysfunction with unstable hemodynamics indicates high-risk massive PE with mortality as high as 50%.[4,6,9,11-13]

The pulmonary vascular and RV response to full spectrum PE severity is very important for PE management and prognosis. However, this has not been fully investigated because a reliable evaluation/examination method to assess RV function in PE is not clinically available, and the difficult accessibility of the pulmonary circulation makes it very hard to obtain pulmonary hemodynamics data in PE patients. Cardiac output (CO) and RV ejection fraction are most commonly used to evaluate RV function, but they are not sensitive enough to detect mild RV compromise in low and intermediate-risk patients. To precisely evaluate cardiac function, pressure-volume (P-V) loops have long been used and remain the gold standard.[14,15] The major advantage of a P-V loop is that it can fully evaluate cardiac mechanics, including contractility, relaxation, pump function, and afterload. Fortunately, animal studies enable the generation of P-V loops and greater accessibility of pulmonary circulation for the evaluation of pulmonary circulatory parameters via pulmonary impedance spectra. To more fully understand PE progression for appropriate clinical management/decision, we evaluated the progressive response of the pulmonary vascular system and RV to full spectrum PE in an acute PE large animal model using P-V loops and pulmonary impedance spectra.

Methods

All animal studies were approved by the University of Kentucky Institutional Animal Care and Use Committee and were conducted in accordance with the Principles of Laboratory Animal Care (National Society of Medical Research) and the "Guide for the Care and Use of Laboratory Animals (National Institutes of Health publication no. 86-23, revised 1996)."

Anesthesia and instrumentation

Crossbred adult female sheep (37-50 kg, n = 8) were intubated following anesthesia induction with ketamine (7 mg/kg) and diazepam (0.5 mg/kg). Anesthesia was maintained with 1% to 3% isoflurane (Narkomed 2B, DRAGER, Telford, PA). Catheters (16 Ga, Intracath, BD Medical Inc., Sandy, UT) were placed into the right femoral artery/vein for arterial blood pressure (ABP)/central venous pressure (CVP) monitoring and fluid administration. A left lateral thoracotomy was performed through the third intercostal space. An 18 mm perivascular flow probe (COnfidence, Transonic Systems Inc. Ithaca, NY) was placed on the pulmonary root for measurement of PA flow (CO) via a flow monitor (TS420 Perivascular Flow Module, Transonic Systems Inc. Ithaca, NY). Another catheter (16 Ga, Intracath, BD Medical Inc., Sandy, UT) was placed in the left atrium for left atrial pressure (LAP) measurement (Figure 1). For high-fidelity PAP measurement, a MICRO-TIP pressure transducer (Transonic Systems, Ithaca, NY) was inserted into the main PA next to the distal side of the flow meter probe. A 5 Fr conductance catheter (Transonic Systems, Ontario, Canada) was then inserted from the RV outflow tract (below PA valve) into the RV toward the apex for P-V loop recording (Figure 1).

Acute PE sheep model and study design

Coarse Sephadex G50 beads (Sigma-Aldrich, St. Louis, MO) with a 100 to 300 μm dry bead size were used. These beads were preswollen with saline to achieve a 200 to 610 μm wet bead size. After animal instrumentation, the bead suspension (250 mg) was injected into the pulmonary circulation via the femoral venous line (Figure 2). Subsequent beads doses (250 mg/dose) were injected every 15 minutes until death from RHF (CO < 0.5 liter/min for 15 minutes). If circulatory collapse (CO < 1.5 liter/min for 5 minutes) occurred immediately after the beads injection, dobutamine (2.5-10 μg/kg/min) was administered to maintain CO and prevent premature death. All

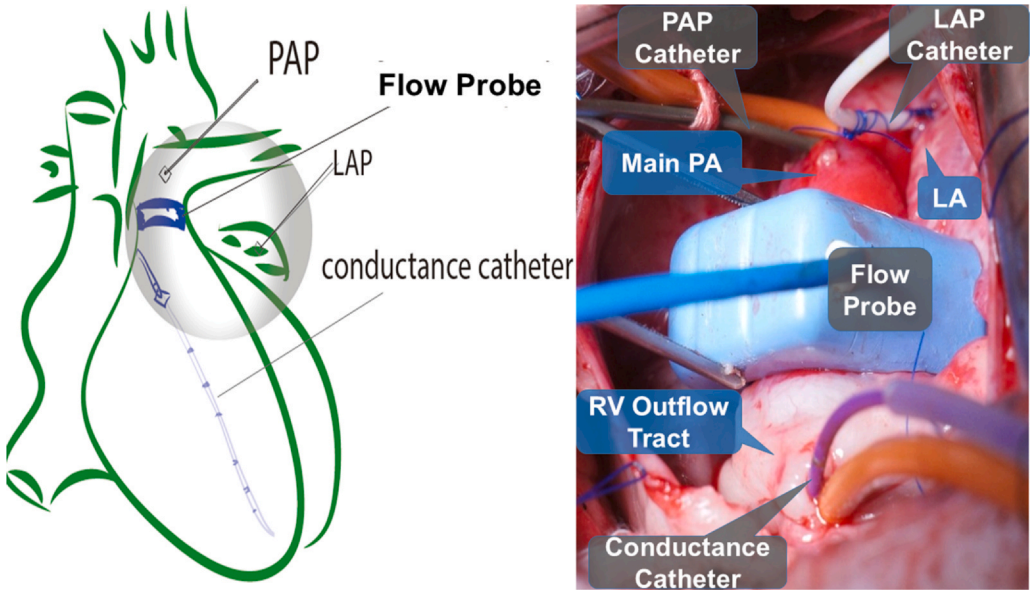

Figure 1 Sheep study instrumentation. A conductance catheter was inserted from right ventricle (RV) outflow tract into RV. Catheters were placed into main pulmonary artery (PA) and left atrium (LA) for PA pressure (PAP) and LA pressure (LAP) measurements, respectively. A perivascular flow probe was placed on the pulmonary root for PA flow (cardiac output) measurement.

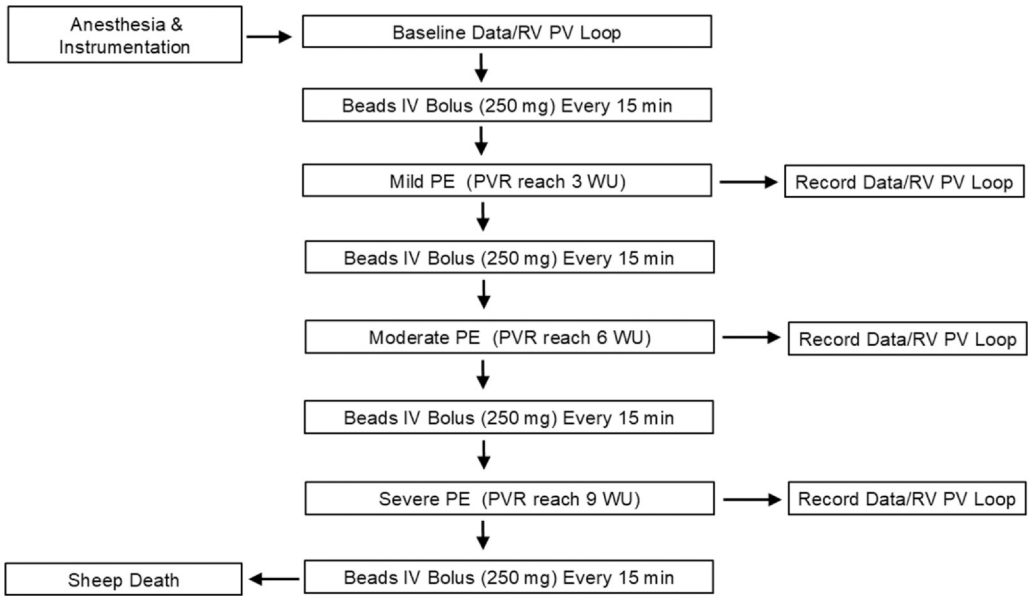

Figure 2 Study design. Following anesthesia and instrumentation, baseline data and right ventricle (RV) pressure-volume (PV) loop were obtained. An intravenous (IV) bolus of beads (250 mg) was then administered every 15 minutes until mild, moderate, and severe pulmonary embolism (PE) was reached as determined by the pulmonary vascular resistance (PVR). Data were recorded at each PE stage.

data were recorded 5 minutes after discontinuing dobutamine to minimize its effect on RV data.

Since increased PVR is the primary PE pathophysiology that affects RV function, PVR was used to stage PE severity into the following groups: (1) baseline (PVR < 3 WU), (2) mild PE (PVR 3-6 WU), (3) moderate PE (PVR 6-9 WU), and (4) severe PE (PVR≥9 WU).

Data acquisition and analysis

Data were collected at baseline (after instrumentation) and when the PVR met the entry criteria for mild (3 WU), moderate, (6 WU), and severe (9 WU) PE.

1. General hemodynamics: The femoral arterial/venous and left atrial catheters were connected to pressure transducers (Edwards Lifesciences, Irvine, CA). The ABP, CVP, LAP, and heart rate were continuously monitored via a Philips MP-50 monitor (Philips Medical Systems, Boeblingen, Germany). The PA blood flow was recorded by a perivascular flow module (T402, Transonic Systems, Ithaca, NY) for CO measurement. The ABP, CVP, PAP, and LAP were recorded by a Quad Bridge Amp (AD Instruments, Sydney, Australia).

2. Impedance and compliance of pulmonary circulation: The pulmonary circulation impedance was calculated

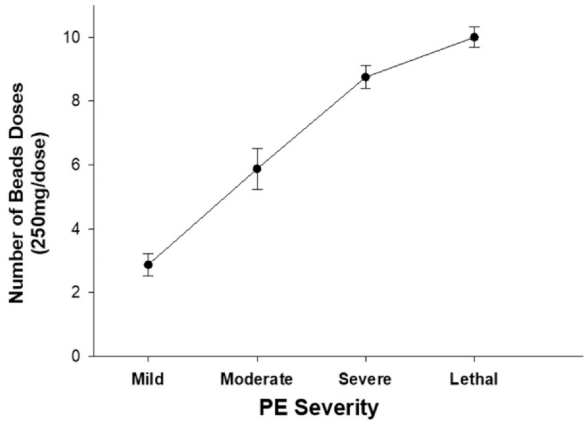

Figure 3 Pulmonary embolism (PE) dose-response relationship. Stepwise administration of 250 mg bead doses led to a progressive increase in PE severity going from mild, moderate, and severe to lethal.

from high-fidelity PAP and PA flow data using Fourier transform (Origin 9.0 Software, OriginLab, Northampton, MA) to generate impedance spectra. The pulmonary vascular impedance at 0 frequency (Z_0) represents static RV load while the impedance at the first harmonic (Z_1) represents RV pulsatile load. The characteristic impedance (Z_c) indicates large vessel compliance.[16,17] Frequency at the first impedance minimum (f_{min}) is a function of pulse wave velocity and distance to major reflection sites. The pulmonary circulation compliance was calculated via the following formula:

SV/PP

where SV is the stroke volume and PP is the pulsatile pressure. PVR was calculated via following formula:

(mPAP – LAP)/CO

3. RV P-V Loop Recording and Analysis: The RV conductance catheter was connected to a Pressure-Volume Control Unit (ADV500, Transonic Systems Inc. Ithaca, NY) to measure the RV P-V loop. These P-V loop data were continuously recorded by a data acquisition system (Powerlab 16/35 system, AD Instruments, Dunedin, New Zealand). The recorded RV P-V loops were analyzed by Labchart Pro V8 and LabChart pro PV-loop software (AD Instruments, Dunedin, New Zealand).

The conductance data were calibrated using the Alpha calibration method.[18] The correction factor alpha was calculated for each measurement comparing CO calculated from the conductance catheter and CO obtained by the perivascular flow probe. A balloon catheter was inserted from the right jugular vein to the inferior vena cava for the calculation of end-systolic elastance (Ees). This balloon was inflated to occlude the inferior vena cava for a temporary decrease of RV preload and deflated to allow progressive preload recovery. A corresponding spectrum of P-V loops was obtained for end-systolic P-V relation. The slope of this line was Ees, which represented RV contractility. The PA elastance (Ea), which represented total RV afterload, was calculated as the ratio of RV end-systolic pressure to stroke volume (SV).[19] The Ees/Ea ratio represented RV-PA coupling.[20] An Ees/Ea > 1.5 indicates optimal RV-PA coupling, 1.5 > Ees/Ea > 1.0 indicates compromised RV-PA coupling, and Ees/Ea < 1.0 is considered RV-PA uncoupling with RHF.[16,21] The RV P-V loop analysis also generated data to reflect RV systolic function (SV, end-systolic pressure [ESP], end-systolic volume [ESV], stroke work, ejection fraction [EF], and dP/dt_{max}) and diastolic function (end-diastolic pressure [EDP], end-diastolic volume [EDV], time constant for isovolumic relaxation [Tau], and dP/dt_{min}).

Statistical analysis

All data were expressed as mean ± standard error of mean. Comparison among baseline, mild, moderate, and severe PE was made with 1-way-repeated measures analysis of variance. All statistical analyses were performed using an SPSS software package (SPSS for Windows 11.5, SPSS Inc, Chicago, IL). A value of $p < 0.05$ was considered statistically significant.

Results

With stepwise intravenous administration of beads (250 mg/dose), all sheep progressed to mild PE (2.9 ± 0.4 doses), moderate PE (5.9 ± 0.6 doses), severe PE (8.8 ± 0.4 doses), and death (10.0 ± 0.3 doses, Figure 3). Up to 3 doses were required to achieve mild PE, which progressed to moderate PE with 3 more doses. With 3 additional doses, PE progressed to a severe stage with RHF. Once the severe PE stage was reached, only 1 extra dose triggered sheep death.

General hemodynamics

At baseline, all hemodynamic parameters were within normal range (Table 1). In mild PE, the mPAP was significantly increased, reaching pulmonary hypertension criteria. Mean ABP (mABP) significantly decreased. CO and CVP were maintained at baseline levels.

In moderate PE, mPAP further increased, and mABP was still significantly lower than baseline. CO was maintained at baseline levels, but CVP was significantly elevated compared to baseline.

In severe PE, mPAP increased even further to over 40 mm Hg. The mABP remained significantly lower than the baseline. CO was significantly decreased while CVP and heart rate were significantly increased. Although the LAP significantly increased only in severe PE, it still remained in normal range.

PVR, compliance, and impedance

PVR was progressively increased through all 3 stages of PE (Table 2). Compared to baseline, PVR increased by 1.7 fold in mild PE, 2.6 fold in moderate PE, and 4.8 fold in severe PE. PA compliance was unchanged in mild PE but decreased significantly in moderate and severe PE compared to baseline. PE also significantly affected the pulmonary impedance spectra

Table 1 Effect of Pulmonary Embolism Severity on Hemodynamics

Parameter	Baseline	Mild PE	Moderate PE	Severe PE
HR (beats/min)	125 ± 6	136 ± 8	134 ± 7	136 ± 5[a]
CO (liter/min)	4.1 ± 0.2	4.0 ± 0.1	3.6 ± 0.4	3.0 ± 0.3[a,b]
mABP (mm Hg)	82 ± 4	65 ± 4[c]	56 ± 5[d]	51 ± 5[d,e]
mPAP (mm Hg)	16 ± 3	26 ± 1[d]	36 ± 1[d,f]	42 ± 2[d,f,g]
LAP (mm Hg)	6.8 ± 0.7	6.9 ± 1.2	7.6 ± 0.9	8.1 ± 0.9[a]
CVP (mm Hg)	8.7 ± 1.4	9.0 ± 1.3	10.8 ± 1.0[a,b]	11.8 ± 1.0[d,e]

Abbreviations: CO, cardiac output; CVP, central venous pressure; HR, heart rate; LAP, left atrial pressure; mABP, mean arterial blood pressure; mPAP, mean pulmonary artery pressure; PE, pulmonary embolism.

[a] $p < 0.05$ versus baseline.
[b] $p < 0.05$ versus mild PE.
[c] $p < 0.01$ versus baseline.
[d] $p < 0.001$ versus baseline.
[e] $p < 0.01$ versus mild PE.
[f] $p < 0.001$ versus mild PE.
[g] $p < 0.01$ versus moderate PE.

(Figure 4). Z_0 and Z_1 were significantly increased in moderate and severe PE (Table 2). Z_c remained unchanged throughout the 3 PE stages. The f_{min} was also significantly increased in moderate and severe PE.

RV P-V loop analysis

A significant change in the RV P-V loop was observed as PE severity increased (Figure 5). At baseline, a normal functioning RV was noted by the triangle-shaped P-V loop in the lower left corner. Progressive PE changed the RV P-V loop in 2 ways: (1) Shape changed from horizontal triangle to upright rectangle. (2) Progressively shifted up and to the right. These P-V loop changes were analyzed to generate data representing RV afterload, systolic function, diastolic function, and RV-PA coupling.

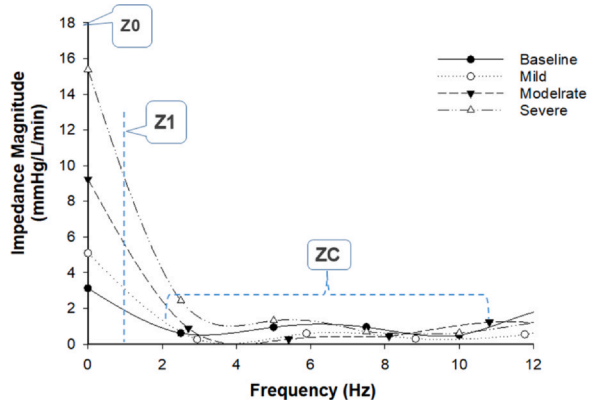

Figure 4 Effect of pulmonary embolism (PE) severity on pulmonary circulation impedance. Static load (Z_0) and pulsatile load (Z_1) were increased in moderate and severe PE groups. Large vessel compliance (Z_c) was unchanged.

Table 2 Effect of Pulmonary Embolism Severity on Pulmonary Circulation

Parameter	Baseline	Mild PE	Moderate PE	Severe PE
PVR (WU)	2.7 ± 0.3	4.7 ± 0.1[a]	7.0 ± 0.3[a,b]	12.9 ± 0.6[a,b,c]
PA compliance (ml/mm Hg)	3.2 ± 0.5	2.8 ± 0.4	1.7 ± 0.3[d]	0.9 ± 0.1[a,b,e]
Z_0 (mm Hg/lliter/min)	4.3 ± 0.3	6.8 ± 0.2	10.1 ± 0.8[f]	16.1 ± 2.0[a,b,e]
Z_1	2.6 ± 0.3	3.8 ± 0.4	5.8 ± 0.6[d]	9.3 ± 1.5[a,b, g]
Z_c	1.9 ± 0.3	1.3 ± 0.2	1.3 ± 0.2	1.5 ± 0.2
F_{min} (Hz)	2.3 ± 0.5	3.8 ± 1.1	5.2 ± 1.8[f]	5.4 ± 2.7[a]

Abbreviations: F_{min}, first impedance minimum; PA, pulmonary artery; PE, pulmonary embolism; PVR, pulmonary vascular resistance; Z_0, pulmonary vascular impedance at 0 frequency (static RV load); Z_1, impedance at first harmonic (pulsatile RV load); Z_c, characteristic impedance (large vessel compliance).

[a] $p < 0.001$ versus baseline.
[b] $p < 0.001$ versus mild PE.
[c] $p < 0.001$ versus moderate PE.
[d] $p < 0.05$ versus baseline.
[e] $p < 0.01$ versus moderate PE.
[f] $p < 0.01$ versus baseline.
[g] $p < 0.05$ versus moderate PE.

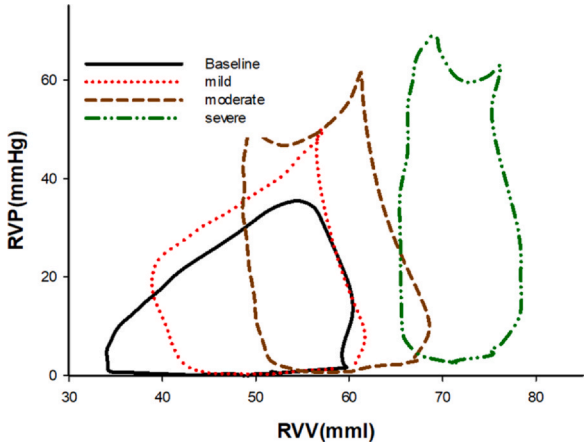

Figure 5 The effect of pulmonary embolism (PE) severity on the right ventricle (RV) pressure-volume (PV) loop. The RV PV loop shifted from left to right and from triangular to rectangular shape with progression from normal to severe PE.

RV afterload

The RV afterload, represented by PA elastance (Ea), was progressively and significantly increased, beginning from mild PE and continuing through severe PE (Table 3).

RV systolic function

In response to steadily rising Ea, RV contractility (ESP, dP/dt_{max}, and Ees) progressively increased through the 3 PE stages (Table 3). ESP and dP/dt_{max} were significantly increased in mild PE. In moderate and severe PE, all 3 RV contractility parameters significantly increased. Regardless of increased RV contractility, the PE-associated Ea elevation gradually increased ESV and decreased SV, stroke work, and EF. These parameters became statistically significant in severe PE. Consequently, CO was only significantly decreased in severe PE.

RV diastolic function

The time constant for isovolumic relaxation (Tau) did not significantly change (Table 3). Despite compensatory increases in dP/dt_{min} in mild to severe PE, the EDP and EDV were gradually increased, representing compromised RV diastolic function. These parameters reached statistical significance in moderate PE (EDP), and severe PE (EDP and EDV).

RV-PA coupling

Ees/Ea (RV-PA coupling) is the capacity of RV contractility (Ees) against total RV afterload (Ea), which represents general

Table 3 Effect of Pulmonary Embolism Severity on Right Ventricle Function

Parameter	Baseline	Mild PE	Moderate PE	Severe PE
RV afterload				
Ea (mm Hg/ml)	0.62 ± 0.04	0.92 ± 0.06[a]	1.41 ± 0.11[b,c]	2.32 ± 0.17[b,c,d]
RV systolic function				
ESP (mm Hg)	29.3 ± 2.5	35.1 ± 3.1[a]	48.1 ± 2.6[b,c]	58.6 ± 2.8[b,c,d]
dP/dt_{max} (mm Hg/s)	1,228 ± 157	1,683 ± 192[a]	2,074 ± 244[b,e]	2,443 ± 318[b,c,f]
Ees (mm Hg/ml)	1.09 ± 0.06	1.32 ± 0.08	1.69 ± 0.08[b,g]	2.08 ± 0.17[b,c,h]
ESV (ml)	39.7 ± 5.2	43.2 ± 5.6	50.9 ± 8.9	69.8 ± 8.5[i,e]
SW (mL.mm Hg)	842 ± 85	831 ± 87	809 ± 86	537 ± 49[a,e,f]
SV (mL)	35.2 ± 2.4	32.8 ± 3.8	29.3 ± 2.4	22.4 ± 1.7[b,g,f]
EF (%)	63 ± 5	58 ± 6	53 ± 4[a]	34 ± 5[b,c,d]
CO (liter/min)	4.1 ± 0.2	4.0 ± 0.1	3.6 ± 0.4	3.0 ± 0.3[a,e]
RV diastolic function				
Tau (ms)	82 ± 7	87 ± 18	76 ± 19	105 ± 39
dP/dt_{min} (mm Hg/s)	−449 ± 87	−590 ± 88	−820 ± 139[b,e]	−1,083 ± 124[b,c,h]
EDP (mm Hg)	6.5 ± 0.7	6.9 ± 0.6	8.1 ± 0.8[a]	10.4 ± 1.3[b,c,h]
EDV(mm Hg)	47.5 ± 3.3	60.4 ± 6.8	73.7 ± 7.5	86.8 ± 10.1[i]
RV-PA coupling				
Ees/Ea	1.79 ± 0.08	1.46 ± 0.12[b]	1.23 ± 0.09[b,g]	0.91 ± 0.08[b,c,d]

Abbreviations: CO, cardiac output; Ea, pulmonary artery elastance (RV afterload); EDP, end-diastolic pressure; EDV, end-diastolic volume; Ees, end-systolic elastance (RV contractility); EF, ejection fraction; ESP, end-systolic pressure; ESV, end-systolic volume; SV, stroke volume; SW, stroke work; PA, pulmonary artery; PE, pulmonary embolism; RV, right ventricle.

[a] $p < 0.05$ versus baseline.
[b] $p < 0.001$ versus baseline.
[c] $p < 0.001$ versus mild PE.
[d] $p < 0.001$ versus moderate PE.
[e] $p < 0.05$ versus mild PE.
[f] $p < 0.05$ versus moderate PE.
[g] $p < 0.01$ versus mild PE.
[h] $p < 0.01$ versus moderate PE.
[i] $p < 0.01$ versus baseline.

RV function. Ees/Ea progressively declined as the PE severity increased (Table 3). Baseline Ees/Ea was greater than 1.5, indicating a healthy RV with optimal RV-PA coupling.[16,21] In mild to moderate PE, the Ees/Ea values suggested borderline optimal compromised RV-PA coupling, respectively. This parameter further decreased to less than 1.0 in severe PE, indicating RV-PA uncoupling and representing RHF with a concurrent significant drop in CO.

Discussion

In this large animal study, incremental PE not only progressively increased PVR, but also decreased PA compliance and increased PA impedance, resulting in a progressive elevation in total RV afterload. To compensate for this increased RV afterload, both RV contractility and relaxation increased. Despite this compensatory mechanism, RV-PA uncoupling with RHF eventually occurred in severe PE. The collapsed RV compensatory system had little tolerance to further PE insults, resulting in fatal hemodynamic collapse with only 1 extra bead dose. In this unstable critical stage, early intervention is crucial for resuscitation. Should be beads dose as multiple beads are in the 250 mg beads dose.

Our acute PE sheep model

Previous large animal PE studies did not assess the full spectrum mild to severe PE progression.[22-24] In our sheep model, small, incremental doses of intravenous beads resulted in a gradual progression from healthy to mild, moderate, severe, and lethal PE in the same animal. This allowed investigation of the RV and pulmonary circulation response across the full spectrum of PE severity.

In this study, real-time RV P-V loops were used to evaluate RV mechanics. One disadvantage of RV-P-V loops is that the RV volume measured by the conductance catheter may not be accurate since the RV geometry is not a typical cylindrical or spherical shape. In this study, to mitigate this problem, concurrent, real-time main PA flow measurements were used to calibrate the P-V loop data.[18] Furthermore, concurrent, high-fidelity PAP and PA flow waveforms enabled the detailed evaluation of PE-induced changes in PA compliance and impedance (RV afterload), which directly affect RV function.

Pulmonary vascular system response to PE

In this in vivo study, beads were used to embolize small PA branches, resulting in a significant increase in PVR and the corresponding decrease in PA compliance. Moreover, there was a sharp increase in Z_0 (static RV load) and Z_1 (pulsatile RV load) as PE progressed from moderate to severe PE. By contrast, Z_c (large artery compliance)[16] was unchanged. This was most likely due to insufficient time for vascular remodeling and collateral formation to develop in acute study.

Compensatory RV response to PE

The elevated PVR/Z_0/Z_1 caused a progressive increase in Ea (RV afterload) and a compensatory increase in RV contractility. In severe PE, a significant increase in ESV and a decrease in RV EF correlated with a significant decrease in CO. RV relaxation (dP/dt_{min}) also increased, but EDV and EDP were still significantly increased in severe PE. Thus, the P-V loop-derived systolic and diastolic parameters are not useful for RV function evaluation in PE because the compensatory increases in RV contractility/relaxation do not reflect global RV function. The EF and CO reflect compromised RV function but were only significantly decreased in severe PE, which is too late to predict PE progression toward RV dysfunction and the need for RV assist.

RV-PA coupling indicates early RV compromise

Despite increased RV afterload, a compensatory increase in RV contractility maintained RV-PA coupling to preserve CO in mild PE. As PE reached the moderate stage, RV decompensation began to occur, resulting in an Ees and Ea mismatch. In severe PE, Ea steeply rose and surpassed continuously increased Ees, causing RV-PA uncoupling.[16,21,20] Correspondingly, the CO also significantly decreased in severe PE. Decreased Ees/Ea has also been found in chronic thromboembolic disease patients.[25] By contrast, other groups saw no significant decrease in Ees/Ea in dog acute PE models, but only the initial stages of PE were examined.[22,24] Our results suggest that Ees/Ea is a reliable and sensitive parameter to predict early progression toward RV compromise in PE. Although it is impractical to routinely install a conductance catheter in PE patients to directly evaluate Ees/Ea, it is practical to use P-V loop-derived Ees/Ea to validate current imaging-derived RV strain parameters to precisely/conveniently indicate Ees/Ea.

Pulmonary circulation compensation in PE

a) First-line compensation from PA: In this study, up to 3 beads doses are required to mildly increase PVR and mPAP to pulmonary arterial hypertension criteria level[26] while maintaining optimal RV-PA coupling. Our data show that the lungs have a large filtering capacity to stop emboli from entering the systemic circulation, but, when exceeded, PE becomes a medical condition.
b) Second-line compensation from RV: The RV can also compensate for PE-induced increase in PVR and mPAP in mild PE. Although PVR and total RV afterload significantly increase, the RV can still maintain borderline optimal RV-PA coupling and normal CO by increasing contractility and relaxation in this stage. In the clinical scenario, those patients may be considered low risk. Therefore, this second-line RV compensation window has a similar capacity as first-line PA compensation.

RV decompensation in PE

As the moderate PE stage was reached, 3 additional beads doses caused progression to severe PE with 1 more dose causing death in all sheep. In the corresponding clinical scenario, RV strain may be detected, and patients are considered intermediate risk. Patients in this stage may still

maintain normal hemodynamics. Additional emboli will induce RV-PA uncoupling and push the patient to severe PE with abnormal hemodynamics (cardiogenic shock), which is equivalent to high-risk PE with very high mortality.

Study limitations

Since the occluding material in clinical PE is usually an active blood clot, our sheep model that used inert beads may not completely reflect the clinical situation. In patients, pulmonary thromboembolism will cause both mechanical obstruction of vessels and release of vasoconstrictive mediators,[27-29] whereas our sheep model only replicated the physical occlusion in PE. In addition, we were unable to fully characterize the resulting vascular obstruction with imaging studies. Our sheep model did, however, allow us to focus on the mechanical obstruction without the robust vasoactive response. Our sheep model with multiple microembolisms also failed to mimic the single macroembolism that typically occurs in patients. Nevertheless, our sheep model enabled the gradual occlusion of vessels for assessment of the full spectrum response to PE. The sheep were also sedated throughout this study, which does not completely reflect the clinical scenario. Moreover, the early decrease in mABP may reflect sheep sedation rather than PE response.

Conclusions

Compensatory increases in RV contractility maintain CO in mild/moderate PE despite RV afterload elevation. Eventually, the increased RV contractility is unable to compensate for elevated RV afterload, resulting in RV-PA uncoupling in severe PE with decompensated RHF. Severe PE rapidly progresses to lethal RHF, which will likely require immediate intervention to prevent death.

Disclosure statement

Drs Dongfang Wang and Joseph B. Zwischenberger receive patent royalties from Getinge and Liva Nova, are co-owners of W-Z Biotech, LLC, and are ASAIO Board members. Drs Dongfang Wang and Cherry Ballard-Croft DW are part-time employees of W-Z Biotech, LLC. Dr Masashi Kawabori is a surgical consultant for Abiomed. All the other authors have no interests to declare.

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