CHEST

Original Research

PULMONARY HYPERTENSION

Prospective Evaluation of Right Ventricular Function and Functional Status 6 Months After Acute Submassive Pulmonary Embolism

Frequency of Persistent or Subsequent Elevation in Estimated Pulmonary Artery Pressure

Jeffrey A. Kline, MD; Michael T. Steuerwald, MD; Michael R. Marchick, MD; Jackeline Hernandez-Nino, MD; and Geoffrey A. Rose, MD

Background: **No published data have systematically documented pulmonary artery pressure over an intermediate time period after submassive pulmonary embolism (PE). The aim of this work was to document the rate of pulmonary hypertension, as assessed noninvasively by estimated right ventricular systolic pressure (RVSP) of ≥ 40 mm Hg 6 months after the diagnosis of submassive PE.**

Methods: **We enrolled 200 normotensive patients with CT angiography-proven PE and a baseline echocardiogram to estimate RVSP. All patients received therapy with unfractionated heparin initially, but 21 patients later received alteplase in response to circulatory shock or respiratory failure. Patients returned at 6 months for repeat RVSP measurement, and assessments of the New York Heart Association (NYHA) score and 6-min walk distance (6MWD).**

Results: **Six months after receiving a diagnosis, 162 of 180 survivors (90%) returned for follow-up, including 144 patients who had been treated with heparin (heparin-only group) and 18 patients who had been treated with heparin plus alteplase (heparin-plus-alteplase group). Among the heparin-only patients, the RVSP at diagnosis was ≥ 40 mm Hg in 50 of 144 patients (35%; 95% CI, 27% to 43%), compared with 10 of 144 patients at follow-up (7%; 95% CI, 3% to 12%). However, the RVSP at follow-up was higher than the baseline RVSP in 39 of 144 patients (27%; 95% CI, 9% to 35%), and 18 of these 39 patients had a NYHA score of ≥ 3 or exercise intolerance (6MWD, < 330 m). Among heparin-plus-alteplase patients, the RVSP was ≥ 40 mm Hg in 11 of 18 patients at diagnosis (61%; 95% CI, 36% to 83%), compared with 2 of 18 patients at follow-up (11%; 95% CI, 1% to 35%). The RVSP at follow-up was not higher than at the time of diagnosis in any of the heparin-plus-alteplase patients (95% CI, 0% to 18%).**

Conclusions: **Six months after experiencing submassive PE, a significant proportion of patients had echocardiographic and functional evidence of pulmonary hypertension.**

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Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; CTPA = CT pulmonary angiography; IQR = interquartile range; NYHA = New York Heart Association; PE = pulmonary embolism; RV = right ventricle/ventricular; RVSP = right ventricular systolic pressure; SBP = systolic BP; 6MWD = 6-min walk distance; V̇/Q̇ = ventilation-perfusion

Submassive pulmonary embolism (PE) is generally defined as a PE that is not severe enough to cause arterial hypotension.[1] Patients with submassive PE can be further stratified based on the presence or absence of abnormalities seen on echocardiography suggesting the presence of right ventricular (RV) strain.[2] The echocardiographic findings that define RV strain in patients with submassive PE, and the optimal treatment of patients with these findings, remain the subject of ongoing debate.[3] Patients with submassive PE treated with heparin followed by oral

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anticoagulation experience a low mortality rate, and many experts think[4–7] that the majority of patients resolve their pulmonary vascular perfusion defects over a period of 6 to 12 months. Although the addition of fibrinolysis to heparin anticoagulation appears to accelerate the resolution of RV dysfunction and to reduce RV systolic pressure (RVSP) in the short term, aggregated data from existing clinical trials[8–11] show no evidence of survival benefit. An important secondary question is whether adjunctive fibrinolysis will improve RV function and reduce RVSP to a sufficient degree to mitigate the symptoms of dyspnea and to improve exercise tolerance in the months after the diagnosis of submassive PE.

Existing studies[4,5,12,13] that have observed survivors of PE for > 3 months have focused on rates of mortality and the severe end point of chronic thromboembolic pulmonary hypertension (CTEPH). These studies have reported an incidence of CTEPH well below 5% within 3 years after PE. No prior study has prospectively observed a cohort of patients with submassive PE, defined using the standard criteria, and reported the outcomes of each patient, including follow-up RV function and estimated pressure, as well as dyspnea severity and exercise capacity.

This report concerns the change in RV strain following submassive PE, as defined by echocardiography. Echocardiographic assessment of RV dilation, RV hypokinesis, and RVSP were measured at diagnosis, and 6 months later, in a prospective cohort of patients with acute submassive PE who were all treated initially with heparin. Twenty-one of these patients were treated with IV alteplase during their hospitalization, and thus were analyzed separately. Specific aims centered on measuring the following end points: (1) change in RV size, function, and RVSP from diagnosis to 6-month follow-up; and (2) New York Heart Association (NYHA) score and 6-min walk distance (6MWD) measured at 6 months after diagnosis. A secondary aim was to assess the interobserver variability for RV size and function, as estimated by echocardiography.

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Affiliations: From the Department of Emergency Medicine (Drs. Kline, Steuerwald, Marchick, and Hernandez-Nino) and the Carolinas Heart and Vascular Institute (Dr. Rose), Carolinas Medical Center, Charlotte, NC.

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Correspondence to: Jeffrey A. Kline, MD, Emergency Medicine Research, Department of Emergency Medicine, Carolinas Medical Center, PO Box 32861, Charlotte, NC 28323-2861; e-mail: jkline@carolinas.org

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Materials and Methods

This study was approved by the Institutional Review Board and Privacy Board at Carolinas Medical Center, a large, urban academic hospital in Charlotte, NC. We prospectively enrolled ED patients and hospital inpatients with confirmed PE from January 2002 until February 2005.

Patient selection

Twice daily, a research coordinator reviewed our hospital electronic order system (IDX Imagecast; GE Healthcare Global; Piscawatay, NJ), for computerized pulmonary angiography and ventilation-perfusion ($\dot{V}/\dot{Q}$) lung scans. A member of the research team located and read the preliminary interpretation by a board-certified radiologist. Inclusion criteria were age > 17 years and a "wet read" interpretation that was positive for acute PE on CT pulmonary angiography (CTPA) or a $\dot{V}/\dot{Q}$ lung scan that was interpreted as indicating a high probability of acute PE.[14] Exclusion criteria included > 12 h since the start of heparin therapy; arterial systolic BP (SBP) < 100 mm Hg; prior study enrollment; current or immediately planned treatment with fibrinolytic therapy, catheter fragmentation, or surgical embolectomy; end-stage illness with either no plan to treat the PE or a do-not-resuscitate order; inability to perform echocardiography; patient-reported baseline inability to walk more than one block; or incarceration.

Study Protocol

Prior to data collection, all patients signed an informed consent form. All patients were treated initially with unfractionated heparin by using a standardized dosing protocol. Immediately after consent, we recorded vital signs, a pulse oximetry reading was obtained with the patient breathing room air for 2 min followed by phlebotomy and echocardiography, which were performed in accordance with a previously described protocol.[15] RVSP was estimated from the Doppler-estimated tricuspid valve regurgitant jet velocity (V), and the equation $RVSP = 10 + 4V^2$. Two cardiologists, blinded to clinical data and each other's interpretations, independently interpreted digitized videos of echocardiograms to provide interobserver agreement data. We used an RVSP of > 39 mm Hg as a definition of pulmonary hypertension, based on expected normal values for patients aged 50 to 59 years, as published by McQuillan et al.[16]

Patients were followed up daily for in-hospital complications. This research protocol recommended fibrinolytic treatment of patients without contraindications in whom either circulatory shock (SBP < 90 mm Hg with signs or symptoms of distress, using previously published definitions[17]) or respiratory failure, defined as the appearance of respiratory distress (unstructured definition) with a pulse oximetry reading of < 90%, developed. The initial escalation in treatment beyond heparin anticoagulation consisted of IV infusion of 100 mg of alteplase (Genentech; San Francisco, CA) over 2 h while heparin was discontinued. The decision to further escalate treatment to catheter fragmentation or surgical thrombectomy was made on a case-by-case basis. At diagnosis, the alveolar dead space fraction; d-dimer concentration; troponin I concentration; factor V and prothrombin gene sequence variations; and lupus anticoagulant, homocysteine, anticardiolipin, anti-β_2 glycoprotein antibody titers were assayed as previously described.[18–20]

We made every reasonable attempt to have all survivors return for repeat assessment 6 months after study enrollment. At the 6-month follow-up visit, patients completed a written survey to assess the NYHA score and answer other questions about functional status.[21] Patients then performed a 6MWD according to published guidelines.[22–24] Transthoracic echocardiography was performed by using the same protocol as at diagnosis. Patients were then followed up for another 6 months to record the results of any subsequent pulmonary vascular imaging that was ordered at the study hospital at the discretion of the patient's personal physician.

Statistical Analysis

Continuous data were examined with the Shapiro-Wilk test, and $p < 0.1$ was used to reject the hypothesis of a normal distribution; the data are presented as the mean ± SD or as the median and interquartile range (IQR). Between-group means for normally distributed data were compared by using an unpaired *t* test, and medians were compared for nonnormal data by using the Mann-Whitney *U* test, with $p < 0.05$ considered significant for either test. We compared the change in estimated RVSP at baseline with that at follow-up between groups by visual plot of pressures, and comparing the proportion of patients who had a decrease (improvement) in RVSP with the proportion who had an increase (worsening) in RVSP by using 95% CIs. Interobserver variability was assessed using the Cohen κ statistic. All statistical testing was performed using a statistical software package (StatsDirect, version 2.6.2; StatsDirect; Cheshire, UK).

Results

We enrolled 210 patients (age range, 18 to 87 years) from January 2002 to May 2005 (Fig 1). The mean time between the initiation of heparin therapy and the performance of the echocardiogram was 13 ± 1 h. Ten patients were excluded from the study shortly after enrollment because of the inability to obtain an echocardiogram (n = 3) or an over-read of the CT angiogram such that the final, written interpretation indicated no evidence of acute PE (n = 7). The per-protocol study cohort thus included 200 patients who had been initially treated with unfractionated heparin, of whom 21 were treated with alteplase. Indications for alteplase therapy included circulatory shock (n = 10), respiratory failure (n = 7), or both (n = 4). Alteplase was infused within 24 h of diagnosis in 18 patients and after 5 h in three patients. Three of the 21 patients treated with heparin and alteplase went on to undergo either catheter fragmentation (1 patient, who subsequently

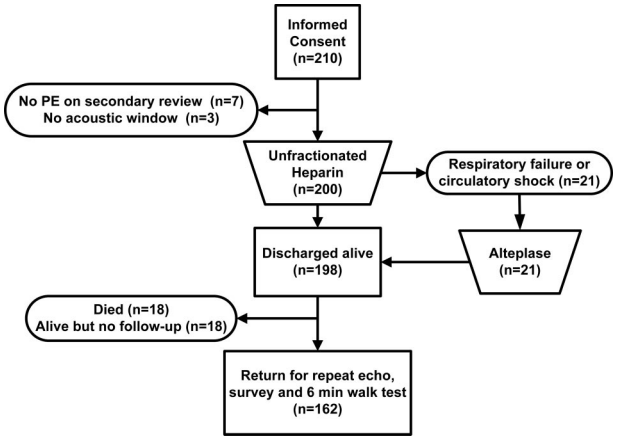

Figure 1. Consort flow diagram showing the outcomes of all patients enrolled.

Table 1—*Baseline Patient Characteristics of Each Treatment Group*

Clinical Features at Study Enrollment	Heparin-Only Group (n = 179)	Heparin-Plus-Alteplase Group (n = 21)
Age, yr*	53 (16)	51 (18)
Female sex†	104 (58)	12 (57)
White race†	102 (57)	13 (62)
Coronary artery disease†	20 (11)	1 (5)
Myocardial infarction†	6 (3)	1 (5)
Heart failure†	12 (7)	2 (10)
COPD†	12 (7)	1 (5)
Prior PE†	13 (7)	3 (14)
Active malignancy†	26 (15)	2 (10)
Body mass index, kg/m^2*	30 (7)	27 (8)
SBP, mm Hg*	132‡ (27)	117‡ (22)
Diastolic BP*	78 (17)	74 (15)
Heart rate, beats/min*	99§ (20)	117§ (19)
Respiratory rate, breaths/min*	22 (5)	25 (8)
Arterial oxygen saturation, %*	94.6 (3.4)	94.2 (4.7)
Troponin T, ng/mL‖	0.00 (0–0.09)	0.01 (0–0.185)
Troponin elevated†	15 (8%)	5 (24)
d-Dimer, μg/mL‖	2.52¶ (1.27–4.52)	7.82¶ (2.75–40.00)
Po_2, mm Hg*	75 (15)	74 (15)
Pco_2, mm Hg*	38 (9)	33 (6)
Alveolar deadspace fraction, %‖	14# (8–25)	50# (40–58)
Total pulmonary vascular occlusion†	49 (34%)	78§ (27%)
Factor V Leiden sequence variation†	15 (8%)	0 (0)
Factor 2 sequence variation†	10 (6%)	4 (19)
Lupus anticoagulant positive†	33 (18%)	5 (24)
β_2-glycoprotein, U/mL*	12.7 (7.1)	14.1 (14.9)
Anticardiolipin IgG, U/mL*	0.24 (0.14)	0.20 (0.12)
Anticardiolipin IgM, U/mL*	0.46 (0.68)	0.43 (0.39)
Anticardiolipin IgA, U/mL*	0.54 (7.08)	0.65 (14.93)
Homocysteine, μmol/L*	12.9 (6.2)	12.8 (7.2)

*Values are given as the mean (SD).
†Values are given as No. (%).
‡$p = 0.02$.
§$p < 0.001$ (unpaired *t* test).
‖Values are given as the median (IQR).
¶$p < 0.001$.
#$p = 0.001$ (Mann-Whitney *U* test).

died) or surgical thrombectomy (2 patients, who both survived). Table 1 presents the clinical features at baseline stratified by treatment. Patients who were treated with heparin and alteplase had a lower mean SBP, higher respiratory and heart rates, median d-dimer concentration and alveolar dead space fraction, and a more extensive clot burden in terms of total pulmonary vascular occlusion.

In-Hospital Outcomes

Three patients treated with heparin alone received dopamine at a dose > 5 μg/kg/min for the treatment of hypotension, and four patients were intubated for respiratory distress, one of whom died. One of the 21 patients treated with heparin and alteplase, who was also treated with attempted catheter fragmentation, died during hospitalization of complications from PE. The remaining 20 patients treated with heparin and alteplase were discharged from the hospital alive without further study-defined complications. No patient in either group experienced intracranial hemorrhage or other bleeding that required a transfusion or surgical intervention. All 198 survivors were treated with oral warfarin sodium therapy that was continued for 6 months.

Echocardiogram Findings at Diagnosis and Follow-up

Eighteen patients died after hospital discharge but before follow-up. Seventeen deaths occurred in pa-

Table 2—*Baseline and 6-Month Follow-up Echocardiographic Characteristics by Treatment Group*

Echocardiographic Findings	Heparin-Only Group		Heparin-Plus-Alteplase Group	
	At Diagnosis (n = 179)	6 Mo Later (n = 144)	At Diagnosis (n = 21)	6 Mo Later (n = 18)
Right ventricle				
Size				
Normal	109 (60)	108 (75)	5 (24)	14 (78)
Dilated	70 (39)	36 (20)	16 (76)	4 (22)
Systolic function				
Normal	143 (80)	134 (93)	9 (43)	17 (94)
Mildly depressed	6 (3)	5 (3)	0 (0)	0 (0)
Moderately depressed	16 (9)	2 (1)	6 (29)	1 (6)
Severely depressed	14 (8)	3 (2)	6 (29)	0 (0)
Tricuspid regurgitation				
None	15 (8)	9 (6)	2 (10)	3 (17)
Mild	134 (75)	124 (86)	9 (43)	15 (83)
Moderate	25 (14)	11 (8)	8 (38)	0 (0)
Severe	5 (3)	0 (0)	2 (10)	0 (0)
RVSP, mm Hg	26* (0–40)	22† (10–30)	45* (29–56)	20† (0–28)
Right atrium				
Normal	129 (72)	119 (83)	10 (48)	15 (83)
Dilated	50 (28)	25 (17)	11 (52)	3 (17)
Left ventricle				
Size				
Normal	166 (93)	141 (98)	21 (100)	17 (94)
Dilated	13 (7)	3 (2)	0 (0)	1 (6)
Systolic function				
Normal	153 (84)	138 (96)	16 (76)	15 (83)
Hyperdynamic	8 (4)	1 (1)	2 (10)	0 (0)
Mildly depressed	8 (4)	2 (1)	1 (5)	2 (11)
Moderately depressed	3 (2)	3 (2)	2 (10)	1 (6)
Severely depressed	7 (4)	0 (0)	0 (0)	0 (0)
Left ventricle ejection fraction, %	54 (11)	56 (7)	55 (9)	54 (6)
Other findings				
IVS flattened or paradoxical	14 (8)	2 (1)	1 (5)	1 (6)
Pericardial effusion	15 (8)	4 (3)	2 (10)	0 (0)
RV/left ventricle diameter	0.83‡ (0.25)	0.73§ (0.14)	1.13‡ (0.34)	0.76§ (0.21)

Values are given as No. (%) or median (IQR). IVS = interventricular septum.
*p < 0.001.
†p = 0.25.
‡p = 0.01.
§p = 0.88 (Mann-Whitney *U* test).

tients in the heparin-only group, 2 of which resulted from recurrent PE; one patient from the heparin-plus-alteplase group died from pneumonia 6 months and 3 weeks after enrollment. No decedent underwent diagnostic evaluation such as echocardiography or right heart catheterization for suspected progressive cor pulmonale from pulmonary hypertension. Eighteen patients were unable or unwilling to return for repeat echocardiography (17 patients from the heparin-only group, and 1 patient from the heparin-plus-alteplase group). Thus, we had complete 6-month follow-up data for 162 of 180 survivors (90%), including 144 patients who had been treated with heparin only and 18 patients who had been treated with heparin plus alteplase (Table 2). The size and function of the RV tended to improve in both groups such that 93% to 94% of patients had normal RV function at 6 months in both groups. In consideration of the RVSP among all 162 patients with follow-up, 12 patients had an RVSP of >39 mm Hg at 6 months (7%; 95% CI, 4% to 13%). Figure 2 plots the RVSP values observed for each patient at baseline and 6 months later according to treatment. When compared with patients treated with heparin alone, patients treated with heparin and alteplase had a significantly larger absolute median decrease in RVSP (-22 mm Hg; IQR, 14 to 32 mm Hg vs -2 mm Hg, respectively; IQR, 0 mm Hg to 26 mm Hg), and a smaller proportion of patients exhibited a net increase in RVSP (0% vs 27%, respectively; 95% CI for difference of 27%, 9% to 35%). Among the 39 patients who demonstrated an increase in RVSP, 1 patient had a left ventricular ejection fraction of $<55\%$ on the second visit. However, if the analysis is restricted to those patients treated with heparin alone and a baseline RVSP of >30 mm Hg (the mean that can be expected for age-matched healthy subjects[16]), this leaves a subgroup of patients ($n = 70$) who had a baseline median RVSP of 43 mm Hg, which is similar to the size of the group treated with alteplase. Fifty-two of these 70 patients had a follow-up echocardiogram, and their median RVSP at 6 months was 24 mm Hg; only 4 patients (9%) had an increase in RVSP. This finding infers the possibility that patients with a higher RVSP at baseline are more likely to show a larger decrease with time, possibly representing a regression to the mean phenomenon.

Outcomes at 6 Months

Within 6 months, as part of standard care (*ie*, not part of a research protocol), 51 patients underwent repeat CTPA scanning (Table 3). Eighteen of these 51 patients had interpretations of "unresolved," "persistent," or "no change" in the filling defect. One patient had a $\dot{V}/\dot{Q}$ scan (without CTPA) that was interpreted as having a low probability for PE. Within 12 months, 40 more patients had a repeat CTPA, 6 of 40 patients had unimproved interpretations, as described, and 1 other patient had a $\dot{V}/\dot{Q}$ scan (without CTPA) with homogenous perfusion. In total, 93 unique patients had a repeat CTPA or $\dot{V}/\dot{Q}$ scan within 12 months of study enrollment, and 24 of 93 patients (26%) had radiologic evidence of unresolved filling defects after the diagnosis of PE. The RVSP was ≥ 40 mm Hg in 2 of 69 patients (3%) with resolved or improving pulmonary vascular filling

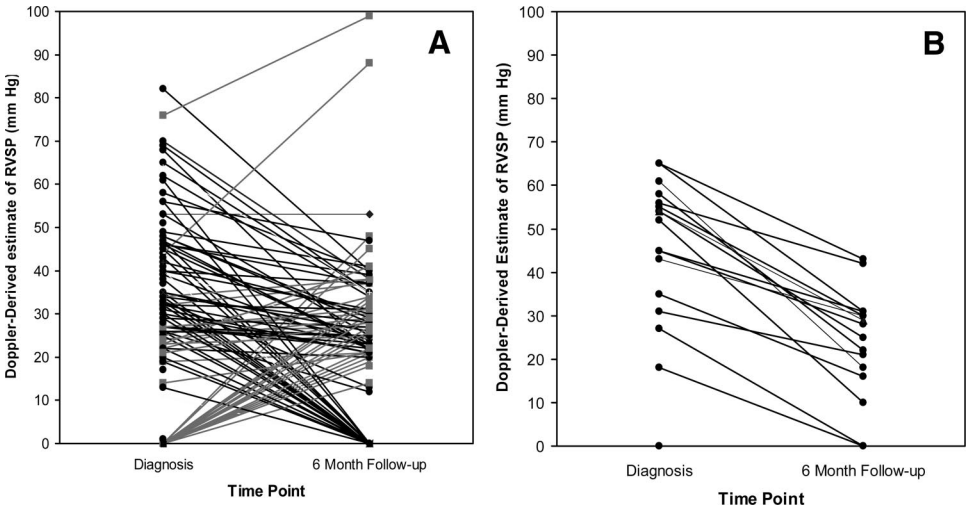

FIGURE 2. Doppler-estimated RVSPs at diagnosis and the 6-month follow-up in (*A*) patients initially treated with heparin alone and (*B*) patients receiving heparin and alteplase. *B*: shows only 16 lines because two patients had an RVSP of 0 at diagnosis and the 6-month follow-up.

Table 3—*Patient Outcomes by Treatment Group*

Outcomes	Heparin-Only Group	Heparin-Plus-Alteplase Group
Alive	159 (89)	19 (95)
Recurrent PE	2 (1)	1 (5)
Returned for follow-up	144 (91*)	18 (95*)
6MWD, m	334 (120)	364 (116)
NYHA score†	144	18
1	64 (44)	11 (61)
2	55 (38)	4 (22)
3	14 (10)	2 (11)
4	8 (6)	1 (6)
6MWD < 330 m or NYHA score > 2	60 (42)	5 (28)
6MWD < 330 m and NYHA score > 2	13 (9)	2 (11)

Values are given as No. (%), unless otherwise indicated.
*Value is given as % of survivors.
†Values are given as the mean (SD).

defects, and the RVSP was ≥ 40 mm Hg in 9 of 24 patients (37.5%) with persistent defects seen on imaging. One of the 24 patients (4%) had been treated with heparin plus alteplase. Two patients (one from each group) received diagnoses of recurrent PE within 6 months. One other patient was considered to have CTEPH by his primary physician.

Neither the 6MWD ($p = 0.10$ [Mann-Whitney *U* test]) nor the distributions of the NYHA scores were significantly different between the treatment groups ($p = 0.49$ [χ^2 goodness of fit]). Among the patients treated with heparin only who had an increase in RVSP (39 patients; 27% of the group), 18 of 39 patients (46%) had either dyspnea at rest or exercise intolerance.

Table 4 reports the interobserver agreement data for the qualitative echocardiographic indexes of RV size, function, and the interventricular septum appearance. The two independent observers had excellent agreement for the interpretation of RV dilation but moderate agreement on the presence or absence of RV hypokinesis.

Discussion

This study extends the current knowledge about the expected course of echocardiographically estimated RV function and pressure after acute submassive PE in patients treated with standard anticoagulation. We measured the change in echocardiographic measurements of RV function and estimated the RVSP at diagnosis and 6 months thereafter in a cohort of 200 patients with clearly defined acute submassive PE. All 200 patients, 21 of whom had their treatment escalated to include alteplase in response to development of circulatory shock or respiratory failure, were normotensive at diagnosis and were treated initially with heparin anticoagulation. Published literature[8–10,25] has shown that the addition of fibrinolysis to standard heparin therapy causes more rapid reduction in perfusion defects and echocardiographic abnormalities of the RV in the first several days after an acute PE. We performed a structured, comprehensive search of prior literature that measured RV function and pressure at a time > 3 months after PE, and found a remarkable dearth of data. As summarized in Table 5, prior to the present report, three studies, comprising a total of 56 patients, had documented the RVSP at baseline and at a follow-up conducted > 3 months after the diagnosis of PE. These studies lacked many important details, including explicit inclusion criteria, information about loss to follow-up, and the patient-oriented end points of dyspnea severity and exercise tolerance.

Our data show a high frequency of unrecognized tricuspid regurgitation suggestive of pulmonary hypertension after submassive PE. However, regardless of treatment, most patients resolved echocardiographic evidence of RV contractile deficits. For example, from the time of diagnosis to the 6-month follow-up, the percentage of patients treated with standard anticoagulation with manifest RV hypokinesis decreased from 20% to 7%, and this same end point among patients treated with heparin and alteplase decreased from 57% to 6%. This degree of improvement in RV hypokinesis remains consistent with the findings of prior studies[9] that included repeat echocardiography within 7 days after diagnosis of PE. However, an unexpected finding was that one-half of our patients treated with standard anticoagulation manifested an increased or persistently elevated RVSP, 46% of whom had either dyspnea at

Table 4—*Interobserver Agreement for Qualitative Echocardiographic Indexes of RV Function After PE*

	At Diagnosis			6 Mo Later		
Echocardiographic Findings	Raw Agreement, %	κ	SEM	Raw Agreement, %	κ	SEM
RV dilated, yes or no	98	0.96	0.085	97	0.89	0.107
RV hypokinesis, yes or no	92	0.76	0.084	90	0.55	0.094
IVS flattened or paradoxical, yes or no	87	0.51	0.081	92	0.65	0.106

See Table 2 for abbreviation not used in the text.

Table 5—*Summary of Predicate Literature Examining RV Pressure Months After PE Treated With Heparin or Fibrinolysis*

Study/Year	Patients, No.	Baseline RVSP, mm Hg	Follow-up Interval	Method of Measuring RVSP	Patients at Follow-up	Treatment in Follow-up Group	RVSP or PAsP at Follow-up, mm Hg	Pulmonary Hypertension, %*
De Soyza and Murphy[30]/ 1972	23	47 ± 12	49 mo	Catheter	13 (57)	Heparin	33 ± 7	69
Hall et al[31]/1977	88	Not reported	2–72 mo	Catheter	14 (16)	Not specified	Not reported	11
Riedel et al[32]/1982	76	Not reported	4.8 yr	Catheter	54 (71)	Not specified	Not reported	22
Schwarz et al[33]/ 1985	7	61 ± 14	15 mo	Catheter	7 (100)	Thrombolytics	24 ± 5	0
Remy-Jardin et al[7]/1997	62	Not reported	8 mo	Echocardiogram	62 (100)	Not specified	Not reported	16
Ribeiro et al[34]/ 1999	78	49 ± 13	12 mo	Echocardiogram	56 (72)	Not specified	Not reported	5
Sharma et al[35]								
2000	21	27 ± 2.0†	7.4 yr	Catheter	11 (52)	Heparin	22 ± 1.4*	55
2000	40	28 ± 1.9†	7.4 yr	Catheter	12 (63)	Thrombolytics	17 ± 1.3*	25
Ciurzynski et al[36]/ 2004	36	48 ± 13	3.1 yr	Echocardiogram	13 (36)	Not specified	24 ± 8	8
Pengo et al[12]/2004	223	Not reported	94.3 mo	Echocardiogram	183 (82)‡	Not specified	Not reported	4
Becattini et al[13]/ 2006	259	Not reported	46 mo	Echocardiogram	37 (14)	Not specified	Not reported	14
Present report								
2008	179	23 ± 21	6 mo	Echocardiogram	144 (80)	Heparin	17 ± 18	19
2008	21	40 ± 21	6 mo	Echocardiogram	18 (85)	Thrombolytics	20 ± 14	22

Values are given as the mean ± SD or No. (%), unless otherwise indicated. PAsP = pulmonary artery systolic pressure.

*Proportion of the patients at follow-up with RVSP > 30 mm Hg or mean pulmonary arterial pressure > 20 mm Hg; and heparin and thrombolytic treatment, respectively.

†Mean pulmonary arterial pressures.

‡At clinical follow-up only; the number of patients with echocardiography data was not stated.

rest or exercise intolerance. Only one patient was thought to have CTEPH, although the protocol was not designed to test for this end point. None of the 18 patients treated with heparin and alteplase demonstrated an increase in RVSP, and 28% of patients had dyspnea at rest or exercise intolerance, despite their generally worse indexes of PE severity in terms of vital signs, gas exchange, biomarkers, and echocardiographic indexes observed at diagnosis. Moreover, the data in Table 1 suggest that differences in outcomes between groups are unlikely to have resulted from differences in underlying thrombophilic or comorbid conditions.

Our data imply that symptom-based, selective monitoring may be an insensitive screening measure for the identification of patients with tricuspid regurgitation suggestive of high right-side heart pressures. Only 9 of 39 patients who manifested an increase in RVSP admitted to dyspnea at rest (NYHA score, 4) at the 6-month follow-up, but 10 more patients admitted to shortness of breath every day with walking. However, we acknowledge that no current clinical guideline would trigger a change in treatment based on the discovery of an elevated RVSP in the absence of severe symptoms or coincident venous thromboembolism recurrence. Nonetheless, abundant preclinical evidence indicates that an elevated RVSP is maladaptive. Experimental pulmonary vascular obstruction causing an RVSP of approximately 45 mm Hg provokes inflammatory injury to the RV that leads to contractile deficits and permanent loss of RV muscle.[26,27] Persistent tricuspid regurgitation may also cause erythrocyte hemolysis, leading to the release of low levels of free heme, and associated vasospasm and inflammation in the lung and other portions of the vasculature.[28,29] The finding of moderate interobserver agreement for the determination of RV hypokinesis provides an additional rationale to use the numeric RVSP to follow RV strain after PE.

Limitations to this report include the fact that the sample was drawn from a single center and included almost only patients with PE diagnosed with CTPA. The data also lack baseline RVSP measurements, the inability to confirm the presence or absence of

diastolic left ventricular dysfunction as a potential confounder, and the absence of catheter-based measurement of the RVSP. We only collected interobserver variability data for the three parameters (dilation, hypokinesis, and inferior vena cava flattening/paradoxical motion), and we only analyzed these parameters as binary (either present or absent). We lack the data to assess the reliability of intraclass interpretations of echocardiograms (*eg*, mild, moderate, and severe hypokinesis), and we do not have interobserver data for other parameters (*eg*, right atrial findings). The causes of dyspnea or exercise intolerance observed 6 months after PE could have been multifactorial, including reasons other than RV dysfunction. Additionally, because we only enrolled patients with diagnostic positive CTPA and $\dot{V}/\dot{Q}$ scan findings, we cannot make any conclusions about patients with nondiagnostic $\dot{V}/\dot{Q}$ scan findings.

In summary, > 90% of the survivors of submassive PE treated with heparin alone exhibited resolution of RV dilation and hypokinesis at the 6-month follow-up, but one-half of patients had unchanged or worsened RVSP, often with associated dyspnea at rest or exercise intolerance. A larger proportion of patients treated with heparin and alteplase manifested decreases in RVSP, but this observation may be explained by their higher RVSP at diagnosis. We conclude that persistent or worsening tricuspid regurgitation suggestive of pulmonary hypertension occurs at a significant rate after acute submassive PE.

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