Association Between Right Ventricular Function and Perfusion Abnormalities in Hemodynamically Stable Patients With Acute Pulmonary Embolism*

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Background/objectives: Patients presenting with acute pulmonary embolism associated with hemodynamic compromise exhibit right ventricular enlargement and dysfunction on transthoracic echocardiogram. However, the degree of echocardiographic abnormalities among hemodynamically stable patients without preexisting cardiopulmonary disease during the acute stage of pulmonary embolism, and following treatment, is unknown. Therefore, this study was designed to assess the extent of right ventricular abnormalities detected on transthoracic echocardiogram in patients following acute pulmonary embolism and during treatment with anticoagulation or vena caval interruption. The extent of pulmonary vascular obstruction and complication rate on follow-up were also assessed.

Design/interventions: Sixty-four consecutive hemodynamically stable patients without preexisting known cardiopulmonary disorder presenting with acute pulmonary embolism and undergoing treatment with anticoagulation or inferior vena caval interruption were studied. All subjects underwent a two-dimensional transthoracic echocardiogram within 24 h of diagnosis. The degree of perfusion abnormality on lung scan was quantified. Twenty-six patients underwent follow-up echocardiogram and lung scan at 6 weeks. The echocardiographic findings were compared with those obtained from a group of normal control subjects matched for gender and age.

Results: Although the mean right ventricular end-diastolic areas did not differ (21.9±5.2 cm² vs 20.1±2.9 cm² for control subjects; p=not significant), the right ventricular end-systolic area was larger in comparison to our series of control subjects (14.6±5.1 cm² vs 11.7±2.0 cm²; p=0.025). Fractional right ventricular area change was reduced in the patient group compared with the control subjects (34.3±9.0% vs 41.3±7.0%; p=0.003). The extent of right ventricular end-systolic area enlargement and decrease in fractional area change did not correlate with the degree of pulmonary vascular obstruction. Patients who were restudied at 6 weeks showed minimal improvement in echocardiographic findings, despite almost complete resolution of perfusion defects on lung scan.

Conclusions: The extent of right ventricular dysfunction in hemodynamically stable, previously normal patients with acute pulmonary embolism does not reflect the extent of the perfusion abnormalities. Further, right ventricular enlargement and systolic dysfunction are present and persistent despite treatment with heparin and warfarin therapy or vena caval interruption.

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Key words: pulmonary embolism; right ventricular enlargement; right ventricular hypokinesis

Abbreviations: DVT=deep venous thrombosis; FAC=fractional area change; PIOPED=Prospective Investigation of Pulmonary Embolism Diagnosis; RVEDA=right ventricular end-diastolic area; RVESA=right ventricular end-systolic area; TR=tricuspid regurgitation; TTE=transthoracic echocardiogram; V/Q scan=ventilation/perfusion scan

A transthoracic echocardiogram (TTE) enables noninvasive and accurate assessment of right ventricular size and systolic function during acute pulmonary embolism.1-3 Further, pulmonary arterial pressure elevations and right ventricular dilatation on echocardiogram in acute pulmonary embolism correlate with the degree of vascular obstruction on pulmonary angiogram in patients with clinically severe pulmonary embolism.3-5 Right ventricular hypokinesis on TTE also has been shown to be associated with greater pulmonary vascular obstruction on ventilation/perfusion (V/Q) scans. Wolfe et al.6 additionally reported that during 14 days of observation...
and heparin therapy, pulmonary embolism recurred only in cases of demonstrated right ventricular hypokinesis on early echocardiogram.2 These studies raise the possibility that TTE may be useful for predicting an adverse course in conventionally treated patients.

Despite the apparent utility of TTE in the assessment of acute pulmonary embolism, it is unclear whether these observations apply to hemodynamically stable patients without preexisting cardiopulmonary disease with acute pulmonary embolism. While most hemodynamically stable patients following acute pulmonary embolism are treated medically and recover uneventfully, some experience significant morbidity such as recurrent embolism and residual respiratory complaints.6,7 If this latter subset could be identified early, then additional monitoring, or treatment besides heparin and warfarin, might be indicated. Therefore, the purposes of this study were as follows: (1) to determine the extent of right ventricular dysfunction among hemodynamically stable patients without preexisting cardiopulmonary disease conventionally treated for acute pulmonary embolism; (2) to determine whether right ventricular dysfunction is associated with a greater degree of pulmonary vascular obstruction; and (3) to determine if acute right ventricular dysfunction is associated with adverse events or persistent echocardiographic or lung scan abnormalities.

Materials and Methods

Subjects

Sixty-four consecutive adult patients admitted to Columbia-Presbyterian Medical Center were included in the study after the following inclusion criteria were satisfied: demonstration of acute pulmonary embolism based on a “high-probability” V/Q scan using Prospective Investigation of Pulmonary Embo\(s\)ism Diagnosis (PIOPED) criteria in the presence of a high index of clinical suspicion \((n=59)\), an “indeterminate” V/Q scan using PIOPED criteria in the presence of a high index of clinical suspicion \((n=1)\). In addition, all patients were in hemodynamically stable condition, defined as not requiring administration of vasopressors to maintain a systolic BP >90 mm Hg. Exclusionary criteria included the following: (1) preexisting uncorrected or active cardiac or pulmonary disease; (2) institution of thrombolytic therapy; (3) need for mechanical ventilatory support; (4) diagnosed pulmonary embolism within the previous year; and (5) duration of symptoms >1 month. An additional six patients were excluded subsequently secondary to suboptimal acoustic window on echocardiogram.

Protocol

This study was approved by the Medical Center’s Institutional Review Board. Potential subjects were identified after two concurring nuclear radiologists interpreted a high-probability or indeterminate V/Q scan, and subsequently notified the investigators. Each case was discussed with the primary physician prior to participation to ensure that a high index of clinical suspicion for acute pulmonary embolism was present. After the patients consented to participate and within 24 h of diagnosis of pulmonary embolism, a two-dimensional TTE was performed and interpreted by echocardiographers blinded to extent of perfusion defects on V/Q scan. Duplex Doppler studies (GE Medical Systems; Milwaukee) of the lower extremities also were performed within 24 h of diagnosis of pulmonary embolism. Patients were treated with heparin followed by warfarin anticoagulation therapy \((n=49)\), anticoagulation and inferior vena cava filter \((n=7)\), or inferior vena cava filter alone \((n=8)\). All therapeutic decisions were made by the primary physicians.

Appropriate levels of anticoagulation were documented in each case for the duration of the study, defined as partial thromboplastin time 1.5 to 2.5 times the upper limit of normal and international normalized ratio of 2.0 to 3.0. Relevant aspects of clinical course (such as recurrences, complications of anticoagulation therapy, deaths) during 6 weeks of follow-up were recorded by the investigators based on chart review and discussion with the primary physicians after hospital discharge. Recurrent pulmonary embolism was defined as new respiratory symptoms accompanied by new mismatched perfusion defects on lung scan.

At 6 weeks from initial diagnosis of pulmonary embolism, both a second V/Q scan and TTE were performed in 26 nonconsecutive patients. Additional testing was conducted earlier if the primary physician determined that this was clinically indicated. Follow-up tests were not performed in cases of interim death \((n=3)\), physical disability prohibiting travel to the medical center \((n=5)\), suboptimal acoustic window on echocardiogram \((n=5)\), and inconvenience or unwillingness to participate further on the part of the patient \((n=25)\). In such cases, interim clinical course or presence or absence of intercurrent significant events (such as symptomatic recurrent embolism) was documented by telephone conversation with the patient or primary physician.

Scoring of V/Q Scans and Echocardiograms

Ventilation and perfusion scintigraphy (Picker International; Cincinnati) was performed using 99m technetium labeled macroaggregated albumin for perfusion and krypton 81-m gas for ventilation studies. The V/Q scans were evaluated with radiograph correlation using PIOPED criteria. At least six projected views were obtained on the perfusion scans, and the information from all views was used to describe the defects. A semiquantitative segmental scoring method described by Parker et al.13,14 was used to score the mismatched perfusion abnormalities. The size of the defect and degree of perfusion reduction were graded individually for each of the 18 anatomic lung segments. These were averaged to calculate the combined percent of pulmonary vascular obstruction. All initial and follow-up V/Q scans were evaluated in randomized order by the same two readers blinded to the clinical information. If interobserver grading was considered discrepant because the total score differed by >10%, then a third reader independently scored the V/Q scan to obtain a mean score.

Two-dimensional echocardiograms and Doppler examinations were performed in all patients (using the HP 1000 or the HP 1500 models; Hewlett Packard; Andover, Mass). The right ventricular end-systolic area (RVESA) and end-diastolic areas (RVEDA) were measured off-line by planimetry in the apical four-chamber view, as previously described.12,13 The measurements were taken as the average of three consecutive cardiac cycles. Fractional area change (FAC) was calculated by the following formula: FAC=\(\frac{(E DA - ESA)}{EDA}\times 100\). Tricuspid re-
gurgitation (TR) was assessed qualitatively as absent, trace, mild, moderate, or severe. A rating of mild or greater was considered positive. All echocardiograms were interpreted by two echocardiographers blinded to the calculated pulmonary vascular involvement and clinical findings. Nineteen age- and sex-matched control subjects underwent similar echocardiograms and these findings were compared with those of the study patients.

**Statistical Analysis**

Significance of differences between initial echocardiogram values obtained in individuals who experienced recurrent thromboembolism and those who did not was assessed using the Mann-Whitney U test for independent groups. Significance of changes between mean initial calculated pulmonary vascular involvement and echocardiogram values and those measured after 6 weeks was assessed using Wilcoxon test for paired observations. Fisher’s Exact Tests were performed to compare differences between observed frequencies of TR and DVT. Significance of the relationship between the initial pulmonary vascular involvement and echocardiogram parameters was assessed by linear regression analysis. Results are presented as means±SD. A p value <0.05 was considered statistically significant.

**Results**

The patient characteristics are summarized in Table 1. Our study population was 70.3% female (45/64), and mean age was 62.8 years. Sixty-one percent (38/62) of patients were diagnosed as having DVT on duplex Doppler examination of the lower (n=60) or upper (n=2) extremities. Six percent (4/64) of patients experienced recurrent pulmonary embolism and 4.7% (3/64) of patients died during the study period (1 from sudden cardiac arrest of unknown etiology, 1 from a cerebral hemorrhage, and 1 from presumed aspiration pneumonia). The mean degree of pulmonary involvement on lung scan in hemodynamically stable patients with acute pulmonary embolism was 37%, which is comparable to the extent of involvement reported by Goldhaber and associates who also employed the method of Parker et al of scoring pulmonary vascular involvement by lung scan.

The RVEDA, RVESA, and FAC measured in our series of normal control subjects (mean age, 63.5±13.2 years; seven men, 12 women) are provided in Table 2. The mean RVEDA measured among our normal control subjects is similar to normal values established by previous investigators. Normal values for RVESA and FAC by this technique are not as clearly established. We also found that previously normal patients with acute pulmonary embolism had significantly greater RVESA and lower FAC compared with our control subjects (14.6±5.1 cm² vs. 11.7±2.0 cm²; p=0.025; 34.3±9.0% vs. 41.3±7.0%; p=0.03; Table 2) as well as more frequent TR (32.8% vs 0%; p=0.002; Table 2). Fifty-eight percent (37/64) of the subjects had an elevated RVESA and 59% (38/64) had a decreased FAC, when normal was defined as within 2 SDs of the mean measured among our series of normal control subjects. There was no significant correlation between the initial degree of pulmonary vascular obstruction and initial RVEDA (r=0.27), RVESA (r=0.34), or FAC (r=0.38), or between the degree of pulmonary vascular involvement and follow-up RVEDA (r=0.35), RVESA (r=0.31), or FAC (r=−0.20). No significant differences were found in mean RVESA, FAC, extent of perfusion abnormality, incidence of TR, or incidence of DVT when the group of four patients who experienced recurrent pulmonary embolism were compared with those with uncomplicated courses (data not shown).

When 26 patients were restudied 6 weeks after their initial presentation, we observed that both the differences in extent of FAC and the prevalence of TR persisted despite substantial resolution of perfusion abnormalities on lung scans (Table 3). These measurements at 6 weeks also remained significantly different from measurements of our control subjects (data not shown). Only in a small subset of patients (n=3) did we find significant increase of both RVEDA and RVESA in the setting of a reduced FAC that was completely reversible by 6 weeks. These cases were associated with greater pulmonary vascular obstruction (68% involvement). The mean degree of pulmonary vascular involvement and right ventric-
In pulmonary hypertension, this reduction in right ventricular ejection fraction mirrors increases in ventricular afterload more so than does the contractile state of the right ventricular myocardium.\textsuperscript{19-22} Similarly, we show in our series that during acute pulmonary embolism, right ventricular systolic function decreases and TR develops. In contrast, the RVEDA, an estimate of right ventricular preload,\textsuperscript{19} does not differ from that of control subjects.

An alternative explanation for the increased TR and normal RVEDA is the presence of right ventricular diastolic dysfunction.\textsuperscript{23} To some extent, the hemodynamic response was variable in this population. In a small subset (n=3), reversible enlargement of both RVESA and RVEDA with a reduced FAC occurred. One explanation is that in some cases and in association with a greater initial clot burden, myocardial contractility can be impaired but capable of complete recovery over time.

Our data suggest that the hemodynamic response may last at least 6 weeks into therapy, even after vascular obstruction by V/Q scan decreases substantially. It is unlikely that undetected recurrent embolism or other forms of heart disease may have contributed to an increase in afterload. The absence of new perfusion defects on follow-up V/Q scans and new cardiac lesions on follow-up echocardiograms argues against this occurrence.

Several limitations in our method warrant consideration. Although we did not find a significant “drop-out bias” statistically, our rate of follow-up was low due mostly to logistical reasons and may have introduced bias. In addition, we relied on duration of symptoms to date onset of acute pulmonary embolism, even though many episodes of pulmonary embolism are asymptomatic.\textsuperscript{24} Since right ventricular enlargement can occur as a response to chronic pulmonary thromboembolic disease, it can be argued that decreased FAC was a hemodynamic response to multiple thromboembolic events over the time preceding our diagnosis of “acute” pulmonary embolism. However, we doubt that cases of preexisting chronic pulmonary embolism confounded our overall results, because the perfusion defects resolved promptly and almost completely on follow-up lung scans; this is more characteristic of acute pulmonary embolism.\textsuperscript{25} Also, while transthoracic echocardiographic evaluation of right ventricular dysfunction may be complicated by frequently encountered inadequate images\textsuperscript{18} and variable sensitivity for detection of pulmonary hypertension,\textsuperscript{26} we attempted to minimize inaccuracies by excluding the few studies that provided suboptimal acoustic windows and ensuring blindness to lung scan and clinical parameters during our measurements. Substantial literature supports the utility of TTE in the characterization of the

\begin{table}[h]
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\begin{tabular}{lccc}
\hline
 & Initial & 6 wk & p Value* \\
\hline
RVEDA, cm\textsuperscript{2} & 22.3±5.8\textsuperscript{1} & 21.5±5.6 & NS \\
RVESA, cm\textsuperscript{2} & 14.9±5.9 & 13.9±5.3 & NS \\
FAC, % & 34.7±10.0 & 36.1±8.8 & NS \\
TR, % of cases & 30.8% & 26.9% & NS \\
Vascular obstruction, % of lung & 34.0±21.9 & 14.3±17.7 & 0.0006 \\
\hline
\end{tabular}
\caption{Summary Data Among 26 Follow-up Cases}

*NS refers to p>0.05.
\textsuperscript{1}Results expressed as mean±SD.
\end{table}
hemodynamic response to pulmonary embolism under specific circumstances, and this study corroborates its role as a noninvasive monitor of right ventricular function in another defined group of patients following acute pulmonary embolism.

The lack of correlation between the extent of pulmonary vascular obstruction on lung scan and echocardiographic parameters was unexpected. One explanation is that even though the degree of pulmonary vascular obstruction measured on pulmonary angiogram correlates well with pulmonary arterial pressures during acute pulmonary embolism, the pulmonary vascular obstruction calculated on lung scan in this study may not necessarily reflect pulmonary arterial pressures. Alternatively, the lack of correlation between echocardiographic parameters and pulmonary vascular obstruction on lung scan demonstrated herein may imply that pulmonary hypertension is more important to the right ventricular response to acute pulmonary embolism than is pulmonary vascular obstruction. Future studies utilizing systematic measurements of pulmonary arterial pressures may help determine whether right ventricular dysfunction by echocardiogram correlates with the degree of pulmonary vascular obstruction or the degree of pulmonary hypertension in previously normal patients with acute pulmonary embolism.

It has been proposed that the threshold for instituting thrombolytic therapy in acute pulmonary embolism should be lowered because these agents accelerate clot lysis. Hemodynamic improvement should be followed with an improvement in pulmonary capillary blood volume in both the short and long term. Further, greater improvement in right ventricular wall motion and right ventricular size have been reported in some populations after thrombolysis, in comparison to after therapy with heparin for acute pulmonary embolism. However, thrombolysis, carries a significant risk of major bleeding estimated at 4 to 15%, and the overwhelming majority of patients in our study (95%) who were treated with either heparin and warfarin anticoagulation or vena caval interruption survived the observation period.

In conclusion, we document that right ventricular enlargement and dysfunction are present and persistent among hemodynamically stable, previously normal patients treated with anticoagulation or vena caval interruption. These abnormalities do not correlate with the severity of pulmonary vascular obstruction.

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