Quantification of right ventricular function in acute pulmonary embolism: relation to extent of pulmonary perfusion defects

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Aims
The relation of the extent of obstruction of the pulmonary vasculature in pulmonary embolism (PE) and impact on right ventricular (RV) hemodynamics is not well established. This study evaluated the relation of size of perfusion defects and changes in echocardiographic measures of global and regional RV dysfunction in 58 consecutive patients with non-massive PE.

Methods and results
Patients were compared with 58 age-matched controls that had normal ventilation/perfusion scintigraphies. A 2D, Doppler and Tissue Doppler echocardiography performed on the same day, quantified RV pressure and global and regional performance. Intermediate and large pulmonary emboli were associated with a significant impact on RV pressure and function. For small pulmonary emboli obstructing $\leq 25\%$ of the pulmonary vasculature, the acceleration time of the pulmonary artery (PA) outflow was significantly shortened, $85 \pm 22$ ms vs. $117 \pm 35$ ms, $P < 0.0001$. Peak systolic strain in the middle segment of RV free wall was reduced in patients with perfusion defect greater than $25\%$, $211 \pm 13$ vs. $213 \pm 17$, $P < 0.001$.

Conclusion
Mid ventricular longitudinal dysfunction consistent with the ‘McConnell-sign’ is found in patients with moderate degrees of perfusion defects, whereas the acceleration time of the PA flow is reduced even in patients with small pulmonary emboli.

KEYWORDS
Pulmonary embolism; Perfusion scintigraphy; Echocardiography; Right ventricle; Ventricular function

Introduction
Pulmonary embolism (PE) is associated with significant mortality and morbidity, especially when associated with right ventricular (RV) dysfunction.1,2 The normal right ventricle is poorly adaptive to sudden increases in after-load and is unable to generate more than moderate increases in RV pressure even when massive obstruction is present.3 The RV pressure is elevated only when $\geq 30\%$ of the pulmonary vasculature is obstructed.3 Earlier reports found an association between measures of RV dysfunction or dilatation and perfusion defects of 20–30%, whereas other studies were unable to identify such a relation.4–7

Submassive PE has been suggested to be present when RV hypokinesia is identified in otherwise haemodynamically stable patients with PE.8 This group has poorer outcome and some studies have shown benefit from fibrinolysis before regular anticoagulation is initiated.1,2,9 A presumably specific feature of significant PE is regional hypokinesia of the mid RV lateral wall10 and later reports have utilize a semi-quantitative approach to the identification of RV dysfunction.1,2 However, with the introduction of Tissue Doppler imaging, regional velocities and systolic deformation can be measured,11 and the normalization of regional RV free wall deformation with thrombolysis has been shown in patients with massive PE.12

The present study investigated the relation of the extent of perfusion defects in patients with PE on quantitative echocardiographic parameters describing RV pressure, dilatation, and global as well as regional function, compared with a group of patients with normal perfusion scintigraphies.

Methods
Patients as well as controls were recruited from a consecutive series of patients referred for V/Q scan on the clinical suspicion of first...
non-massive PE. For the present analysis, patients with PE were compared with an age-matched control group with normal V/Q scan from the same population. The local scientific Ethics Committee approved the study, reference no. KA 03035.

V/Q scan

V/Q scan was performed by injection of 110 MBq of 99mTechnetium macro-aggregated albumin (Lyo MAA, Malinckrodt, The Netherlands) and planar imaging was performed using a large field of view gamma camera (Genesys, ADAC Laboratories, Milpitas, CA, USA) during inhalation of 81Kr-Krypton (dual isotope technique). Posterior, anterior, left and right posterior oblique scintigrams were acquired to a total of 100 counts or 300 s in each position.

Two expert readers, blinded to the clinical and echocardiographic information, classified the extent of perfusion defects as: absent (0%), small (1-25%), intermediate (25-49%), or severe (>50%). The diagnosis of PE (high probability) was made according to the revised PIOPED criteria in 58 patients,14,15 and patients with normal scans (no ventilation or perfusion defects) were included as the reference group in the present analysis, omitting patients with indeterminate scans (defined as intermediate or low probability) from further analysis. Differences in the initial assessment were resolved by consensus re-evaluation of the scans.

Echocardiography

Transthoracic echocardiography was performed using a Philips SONOS 7500 system (Bothell, WA, USA) on the same day as the V/Q scan with a median delay of 1.6 h, maximal 5.6 h. 13

Measures of RV anatomy were RV end-diastolic diameter, measured in the parasternal long axis view, and the ratio of RV to left ventricular end-diastolic diameter (RV/LV ratio) in the apical four-chamber view.16

Measures of RV pressure were the acceleration time of the RV outflow, i.e. the pulmonary artery (PA) acceleration time, measured by pulsed wave Doppler with the sample volume positioned at the pulmonary valve in the parasternal short axis view17 and the RV systolic pressure estimated by continuous wave Doppler by maximal pressure gradient of the tricuspid regurgitation.18 Presence of abnormal motion of the interventricular septum in diastole as a sign of RV diastolic pressure exceeding LV diastolic pressure was also recorded.

Measures of RV function included the diameter of the fractional shortening of the RV outflow tract diameter measured by M-mode echocardiography in short axis view at the level of the aortic valve and the fractional shortening of the RV in the parasternal long axis.16 In the apical four-chamber view, the tricuspid annular plane systolic excursion (TAPSE) and the peak systolic velocity (s') was measured by M-mode and pulsed wave Tissue Doppler imaging, respectively, at the junction of the RV free wall and tricuspid annular plane. The RV index of myocardial performance was calculated as the sum of the isovolumic contraction and relaxation interval, divided by the ejection time as determined by Doppler echocardiography.19 A colour TDI cine loop of three consecutive cardiac cycles of the RV free wall was acquired in the apical four-chamber view and stored for off-line analysis. Average frame rate was 120 ± 12 frames per second.13 Using the Philips Qlab software, version 2.0 (Bothell, WA, USA), an anatomical M-mode line was placed in end-systole, and the peak systolic velocity and strain of the basal and mid third of the RV free wall were recorded. Acquisition of images and subsequent analysis of echocardiographic imaging was performed blinded to the findings at the V/Q scan. Left ventricular ejection fraction was estimated from 16-segment wall motion score analysis.16 The intra- and inter-observer coefficients of variation of the M-mode based measurements were 4 and 8%, respectively, whereas the coefficient of variation in the Tissue Doppler-based measurements of myocardial velocities and strain were 12%.20

Clinical and biochemical data

Information on previously established risk factors and prior chronic obstructive pulmonary disease were obtained from the patients charts, blinded to the findings at the scintigraphy and echocardiography, and the Wells pre-test risk score was calculated.13,21 Electrocardiographic signs of RV strain, defined as presence of Right Bundle Branch Block, S_IIQ_III_T III -sign or negative T-waves in V₆-V₁ on electrocardiograms were recorded if ECG performed within 24 h of the V/Q scan was available. Peak D-dimer levels (STA-LIATEST D-Di, Diagnostica Stago Inc., Parsippany, NJ, USA) and Troponin-T levels (Roche Diagnostics, Denmark) within 3 days of the V/Q scan were also included.

Statistical analysis

To avoid potential bias from differences in age in the groups analysed, a 1:1 matching of the 58 cases with PE to patients with normal V/Q scans was performed.

Data are presented as number and/or percentage for categorical variables, and mean and standard deviation for continuous variables: differences were tested by χ² test or in an ANOVA model with Bonferroni corrected P-values, and linear trends were analysed with F-test and Cochran-Armitage trends tests, as appropriate.

A P-value <0.05 was considered statistically significant in all calculations. All computations were done using the SAS statistical software, version 9.12, SAS Institute Inc., Cary, NC, USA.

Results

Mean age in the population studied was 70 ± 15 years and 51% were male. All patients included were referred for V/Q scan based on a clinical suspicion of PE, but no differences in symptoms or clinical characteristics in relation to the presence or extent of perfusion defects were observed (Table 1). The extent of perfusions defects was not associated with higher pre-test probability level or the Wells score (data not shown). Co-existing chronic obstructive pulmonary disease or reduced left ventricular function was equally distributed among PE patients and controls, 7 (12%) vs. 6 (10%), NS and 6 (10%) vs. 9 (16%), NS, respectively, with no significant skew in the distribution according to extent of PE (data not shown).

The echocardiographic findings are shown in Table 2, where a significant relation of size of the PE and measures of RV size, pressure, and function was found, except for the RV index of myocardial performance and the peak tricuspid annular systolic velocity (s’). A significant increase in estimates of RV pressure with increasing extents of perfusions defects was found, and the PA acceleration time, in particular, was shortened even in patients with small emboli, 85 ± 22 ms vs. 117 ± 35 ms, P < 0.05. TAPSE was inversely related to size of PE, P_trend = 0.0008, although no significant change could be observed in patients with smaller PE. Abnormal septal motion was observed in 2 (8%), 10 (45%), and 7 (64%) of patient with small, intermediate, and severe perfusion defects, respectively, P<0.001 & trend < 0.0001.

The regional myocardial velocities in the basal and mid free wall segments were not related to the extent of PE, whereas significantly lower values of RV systolic strain were observed in the middle myocardial segment, −1 ± 13% vs. −13 ± 17%, P < 0.05 (Table 2). Lower levels of strain were present only in patients with 25-49% perfusion defects, P < 0.001, whereas the difference in the small group with the largest defects did not reach statistical
Right ventricle function in pulmonary embolism

Table 1. Characteristics of patients with normal V/Q scans and patients with pulmonary embolism stratified by size of the perfusion defect on V/Q scans.

<table>
<thead>
<tr>
<th>Perfusion defect</th>
<th>Normal V/Q scan</th>
<th>Pulmonary embolism</th>
<th>P-value ANOVA†</th>
<th>P-value trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
<td>&lt;25%</td>
<td>25–49%</td>
<td>≥50%</td>
</tr>
<tr>
<td></td>
<td>n = 58</td>
<td>n = 24</td>
<td>n = 23</td>
<td>n = 11</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>32 (55%)</td>
<td>13 (54%)</td>
<td>10 (44%)</td>
<td>4 (36%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69 ± 15</td>
<td>75 ± 15</td>
<td>69 ± 16</td>
<td>69 ± 17</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27 ± 5</td>
<td>24 ± 4</td>
<td>26 ± 4</td>
<td>26 ± 6</td>
</tr>
<tr>
<td>Any risk factor presentb</td>
<td>23 (40%)</td>
<td>8 (33%)</td>
<td>13 (57%)</td>
<td>4 (36%)</td>
</tr>
<tr>
<td>Dyspnoea present</td>
<td>42 (75%)</td>
<td>18 (75%)</td>
<td>20 (95%)</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>Sign of DVT</td>
<td>22 (38%)</td>
<td>8 (33%)</td>
<td>11 (48%)</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>143 ± 28</td>
<td>128 ± 30</td>
<td>137 ± 24</td>
<td>131 ± 22</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81 ± 16</td>
<td>78 ± 17</td>
<td>86 ± 16</td>
<td>75 ± 10</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>80 ± 18</td>
<td>77 ± 17</td>
<td>85 ± 16</td>
<td>79 ± 9</td>
</tr>
<tr>
<td>RV strain on ECGc</td>
<td>5 (11%)</td>
<td>7 (30%)</td>
<td>10 (48%)</td>
<td>8 (72%)</td>
</tr>
<tr>
<td>Peak D-dimer (mmol/mL)</td>
<td>3.4 ± 4.7</td>
<td>7.4 ± 7.0</td>
<td>9.4 ± 7.3*</td>
<td>11.3 ± 7.8*</td>
</tr>
<tr>
<td>Peak Troponin-T (U/mL)</td>
<td>0.1 ± 0.5</td>
<td>1.0 ± 3.4</td>
<td>0.1 ± 0.2</td>
<td>0.3 ± 0.5</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>54 ± 11</td>
<td>53 ± 11</td>
<td>55 ± 7</td>
<td>59 ± 3</td>
</tr>
</tbody>
</table>

†Chi-square test used for categorical variables.

Table 2. Echocardiographic findings in patients with pulmonary embolism by extent of perfusion defect and compared to patients with normal V/Q scans. Data presented as mean ± SD and differences in groups tested by ANOVA and assessment of linear trend.

<table>
<thead>
<tr>
<th>Perfusion defect</th>
<th>Normal V/Q scan</th>
<th>Pulmonary embolism</th>
<th>P-value ANOVA</th>
<th>P-value trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
<td>&lt;25%</td>
<td>25–49%</td>
<td>≥50%</td>
</tr>
<tr>
<td></td>
<td>n = 58</td>
<td>n = 24</td>
<td>n = 23</td>
<td>n = 11</td>
</tr>
<tr>
<td>2D and Doppler echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV end-diastolic diameter (cm)</td>
<td>2.9 ± 0.5</td>
<td>3.0 ± 0.7</td>
<td>3.4 ± 0.9*</td>
<td>3.3 ± 0.6</td>
</tr>
<tr>
<td>RV to LV diameter ratio</td>
<td>0.74 ± 0.15</td>
<td>0.85 ± 0.20</td>
<td>1.06 ± 0.44*</td>
<td>1.04 ± 0.23*</td>
</tr>
<tr>
<td>TR max pressure gradient (mmHg)</td>
<td>28 ± 10</td>
<td>32 ± 12</td>
<td>38 ± 14*</td>
<td>45 ± 12***</td>
</tr>
<tr>
<td>PA acceleration time (ms)</td>
<td>117 ± 35</td>
<td>85 ± 22*</td>
<td>85 ± 24*</td>
<td>78 ± 25*</td>
</tr>
<tr>
<td>RV diameter fs (%)</td>
<td>22 ± 11</td>
<td>20 ± 10</td>
<td>12 ± 12*</td>
<td>17 ± 13</td>
</tr>
<tr>
<td>RV outflow tract fs (%)</td>
<td>39 ± 14</td>
<td>32 ± 13</td>
<td>27 ± 12*</td>
<td>30 ± 14</td>
</tr>
<tr>
<td>TAPSE (cm)</td>
<td>2.1 ± 0.6</td>
<td>2.0 ± 0.5</td>
<td>1.8 ± 0.5</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>TV peak annular systolic velocity (cm/s)</td>
<td>15 ± 4</td>
<td>13 ± 3</td>
<td>13 ± 4</td>
<td>12 ± 5</td>
</tr>
<tr>
<td>RV index of myocardial performance</td>
<td>0.32 ± 0.18</td>
<td>0.50 ± 0.25*</td>
<td>0.41 ± 0.33</td>
<td>0.45 ± 0.16</td>
</tr>
<tr>
<td>LV end-diastolic diameter (cm)</td>
<td>5.1 ± 0.8</td>
<td>4.8 ± 0.7</td>
<td>4.3 ± 0.8</td>
<td>3.9 ± 0.8</td>
</tr>
<tr>
<td>Tissue Doppler imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak systolic velocity, basal segment (cm/s)</td>
<td>6.9 ± 3.5</td>
<td>6.2 ± 2.6</td>
<td>6.3 ± 3.0</td>
<td>7.0 ± 2.4</td>
</tr>
<tr>
<td>Peak systolic velocity, mid segment (cm/s)</td>
<td>5.7 ± 3.0</td>
<td>4.1 ± 1.9</td>
<td>5.8 ± 3.2</td>
<td>6.5 ± 1.9</td>
</tr>
<tr>
<td>Peak systolic strain, basal segment (%)</td>
<td>−18 ± 24</td>
<td>−15 ± 23</td>
<td>−15 ± 17</td>
<td>−16 ± 8</td>
</tr>
<tr>
<td>Peak systolic strain, mid segment (%)</td>
<td>−13 ± 17</td>
<td>−13 ± 17</td>
<td>−1 ± 13*</td>
<td>−7 ± 12</td>
</tr>
</tbody>
</table>
| RV, right ventricle; LV, left ventricle; TR, tricuspid regurgitation; PA, pulmonary artery; TAPSE, tricuspid annular plane systolic excursion; TV, tricuspid valve.  
*P < 0.05 compared with patients with normal V/Q scans. 
**P < 0.05 compared with patients with small perfusion defects, i.e. <25%.

Discussion

Significant deterioration of RV function occurs only with moderate size PE, defined as perfusion defects of more than 25%. A significant relation of increased RV systolic pressure and extent of perfusion defects exists, and the PA acceleration time seems to be the more sensitive marker for evaluation of RV function.

By semi-quantitative assessment of wall motion of the mid RV free wall in patients with perfusion defects ≥50%, normal RV function was seen in five patients, whereas six patients had RV dysfunction, most of which (n = 5) has RV mid-wall akinesia. The corresponding mean strain values were −19 ± 5 and 2 ± 7%, respectively, PANOVA = 0.002.
of pressure overload, especially in patients with small PE. Decreased regional systolic deformation of the mid RV free wall, consistent with the so-called McConnell-sign, is seen in patients with perfusion defect of more than 25%.

The present study applies quantitative, modern echocardiographic markers of RV pressure and function in the analysis of the relation of size of PE and RV overload. Previous studies have shown that the RV is unable to generate RV pressures of more than 40–50 mm Hg in this situation, and RV failure is imminent. Signs of global RV failure are present in about a third of patients with non-massive PE. The present study found that the acceleration time was reduced even in patients with small PE, suggesting that this parameter is the more sensitive parameter for the evaluation of RV pressure overload, even when no signs of RV failure are present.

Previous studies have stated that PE associated with <20–30% perfusion defects on V/Q scans is rarely associated with RV failure. Therefore, we chose a cut-off of 25% for identification of patients with smaller PE in the present study. RV dilatation is identified in patients with larger PE, which is also confirmed in the present study.

In the present study, small PE were not associated with significant changes in any of the quantitative measures of RV dysfunction studied, even though a consistent trend of impact was seen for all measures. We were able to confirm that PE obstruction more than 25% of the pulmonary vascular tree is associated with RV failure, with changes in all the measures of global RV functions tested. Interestingly, further deterioration in RV dysfunction was not consistently observed in the small subgroup of patients with large PE obstructing more than 50% of the vascular tree.

As most earlier studies applied a semi-quantitative or qualitative approach in the evaluation of RV dysfunction, a more quantitative approach to evaluation of global and regional RV function has only been applied in a limited number of studies.

The evaluation of regional RV dysfunction applying the Tissue Doppler-derived measures of RV deformation seems to confirm the existence of a supposedly specific feature of PE: mid ventricular RV systolic dysfunction. The changes observed by McConnell et al. were assessed by analysing the radial motion of the RV free wall in different degrees of severity of disease. We found that in patients with severe PE, systolic longitudinal deformation was reduced, although the reduction was not statistically significant. By stratification of patients by presence of radial RV dysfunction, strain was found to be lower in patients with smaller PE, suggesting that this parameter is the more sensitive parameter for the evaluation of RV pressure overload, even when no signs of RV failure are present.

The present study was performed in a sample of patients from a consecutive series of patients referred for V/Q scan on the clinical suspicion of a first non-massive PE, omitting patients with indeterminate scans. Matching of patients with PE and control subjects by age eliminated potential bias, and since the clinical characteristics of patients with normal V/Q scans and patients with PE were not different, confounding of the results related to the impact of extent of perfusion defects is unlikely. Patients with normal scans constituted the control group avoiding comparison with normal healthy volunteers and thereby potentially increasing the clinical relevance of the findings. The extent of perfusion defects was graded into three groups avoiding variability of scoring the scans quantitatively, and to resemble every day clinical practice, and was found to be strongly related to levels of D-dimer.

The apical segment of the RV was not included in the Tissue Doppler analysis because of lower feasibility and the possibility that RV dilation associated with PE would induce a systematic bias.

Conclusions

Global RV dysfunction occurs in patients PE associated with moderate and severe outflow obstruction defined as perfusion defects of 25% or more. Mid ventricular myocardial longitudinal dysfunction, as quantified by Tissue Doppler-derived deformation analysis, is seen in patients with moderate degrees of pulmonary vascular obstruction.

The acceleration time of the PA outflow seems to be affected in patients with small PE and may thus be the more sensitive parameter in the echocardiographic assessment of RV pressure overload.

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Conflict of interest: none declared.

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Right ventricle function in pulmonary embolism


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