Prognostic importance of quantitative echocardiographic evaluation in patients suspected of first non-massive pulmonary embolism

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Aims Patients suspected of acute pulmonary embolism (PE) frequently undergo echocardiography as a part of the initial work-up. Prognostic implication of routine echocardiography in patients suspected of PE remain to be established.

Methods and results Transthoracic echocardiography, including tissue Doppler imaging, was performed in 283 consecutive patients referred for ventilation/perfusion scintigraphy (V/Q scan) on suspicion of first non-massive PE. The prognostic information of quantitative measures of right ventricular (RV) size, function, and pressure was assessed. Patients with PE had a follow-up echocardiography after 1 year and changes in the parameters were assessed.

Patients with PE and normal V/Q scans had similar age-adjusted 1 year mortality [10 and 12%, NS (not significant)], although patients with indeterminate scans carried a poorer prognosis (16% survival, \( P = 0.0004 \)). Among all patients left ventricular (LV) ejection fraction as well as shortening of the pulmonary artery (PA) acceleration time (a measure of RV after-load) was associated with increased mortality [hazard ratio (HR) = 0.84 per 10 ms increase, \( P < 0.0001 \)].

In patients with confirmed PE, the PA acceleration time is predictive of event-free survival (all-cause mortality and heart failure hospitalizations) adjusted for LV ejection fraction, age, and sex (HR = 0.78 per 10 ms increase, \( P = 0.04 \)).

Measures of regional myocardial function were not related to outcome in this study, regardless of presence of PE.

Conclusion PA acceleration time and LV systolic function are independent predictors of mortality in patients suspected of PE, and are independent predictors of event-free survival in patients with confirmed PE.

Introduction

Although not established as a diagnostic tool in the initial management of patients suspected of non-massive pulmonary embolism (PE), transthoracic echocardiography (TTE) provides data for risk stratification if PE is found, including identifying patients who might benefit from more aggressive treatment and is useful for the assessment of important differential diagnoses. Furthermore, the literature of the natural history of patients with non-massive PE is limited.

Several quantitative echocardiographic measures of right ventricular (RV) function and pressure estimation have been validated in previous studies. Among measures of RV pressure, the pulmonary artery (PA) acceleration time is known to be inversely correlated to RV mean pressure, and this parameter has been shown to be a marker of proximal pulmonary emboli. Several echocardiographic parameters associated with increased risk in PE have been identified, but the prognostic implications of early TTE in patients suspected of PE has only been assessed in one earlier study, and the prognostic information available with the newer quantitative echocardiographic parameters has not been evaluated.
The present study assesses long-term survival and clinical course of patients suspected of first non-massive PE. Secondly, in patients in whom PE were present, a follow-up echocardiography was performed to assess the natural history of RV size, pressure, and function in patients treated for PE.

Methods

The study population consisted of 283 consecutive, clinically stable patients over the age of 18 years, referred for ventilation/perfusion scintigraphy (V/Q scan) to establish the diagnosis of first non-massive PE at the Copenhagen University Hospital Gentofte, and has previously been described. The local scientific ethical committee approved the study, reference no. KA 03035, and patients consented to the inclusion as well as follow-up. Information on medical history was obtained from the patients charts, blinded to the findings at the scintigraphy and echocardiography.

Ventilation/perfusion scintigraphy

V/Q scan was performed by injection of 110 MBq of Technetium 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 Krypton (dual isotope technique). Posterior, anterior, left and right posterior oblique scintigrams were acquired to a total of 10¹ counts or 300 s in each position. Two expert readers, blinded to the clinical and echocardiographic information, classified the scans according to the revised PIOPED criteria and estimated the extent of perfusion defects in patients with PE as: small (1–25%), intermediate (25–49%) or severe (>50%).

Echocardiography

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

Measures of RV anatomy were RV end-diastolic diameter, measured in the parasternal long-axis view, and the ratio of RV to left ventricular (LV) end-diastolic diameter (RV/LV ratio) in the apical four-chamber view. 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 Doppler imaging (TDI), respectively, at the junction of the RV free wall and tricuspid annular plane. 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/s. Using the Philips Q-lab 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.

Electrocardiographic data

Electrocardiographic signs of RV strain, defined as the presence of right bundle branch block, S“Q“R“T=sign or negative T-waves in V₁–V₃ on electrocardiograms were recorded if ECG performed within 24 h of the V/Q scan was available.

Follow-up

Follow-up was done via data linkage to the Central Person Register at the end of February 2007 for the assessment of all-cause mortality at 1 year and at end of follow-up (median follow-up time 3.1 years). One patient had emigrated prior to inclusion, and was excluded from the present analysis as no survival data could be obtained, leaving 282 patients for further analysis. A sub-group analysis in patients with PE was planned, and due to an expected limited number of deaths in the cohort at 1 year, a predefined secondary end-point of heart failure hospitalization or death was assessed from data linkage to the Danish administrative hospital registry at 1 year.

All patients alive were contacted by telephone 1 year after their inclusion in study (median 365 days, inter-quartile range: 3 days), and a structured interview was performed including information of current functional capacity, defined as New York Heart Association class, and hospitalizations after discharge from hospital. At the end of the interview, patients with PE were offered a clinical visit, including TTE and ECG. TDI data were not available at follow-up.

Statistical analysis

Data are presented as mean ± SD, differences were tested by paired or un-paired t-test as appropriate. Changes in paired categorical data were evaluated by McNemar’s test. Age-adjusted Kaplan-Meier plots are presented for univariate survival analysis at 1 year and at end of follow-up, differences in survival rates were tested by log-rank test. A Cox proportional hazard model for multivariable analysis was used for univariate and multivariate modelling (backward elimination), after checking for assumptions of proportionality, linearity, and lack of interactions. As the PA acceleration time has been shown to be related to heart rate, all analyses were repeated correcting of heart rate. 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 68 ± 16 years, and 53% were female. Chronic obstructive pulmonary disease was present in 52 (19%) patients at baseline, and was significantly more prevalent in patients with indeterminate V/Q scans than in patients with normal scans or PE, 30 vs. 10 and 12%, P = 0.0002, although presence of chronic obstructive pulmonary disease had no effect on overall mortality, log-rank test P = 0.17. No differences in blood pressure, heart rate, symptoms suggestive of or prevalence of risk factors associated with PE, was found between the three groups of patients defined by the findings at V/Q scan.

Follow-up on patients referred for ventilation/perfusion scintigraphy

Overall 46 (16%) patients had died before 1 year follow-up could be obtained, and in 14 patients no interview could be performed: nine patients refused, two were unable to participate due to medical conditions, and we were unable to contact three patients, Figure 1.
Among 222 patients available for the follow-up interview, 33 (37%), 31 (36%), and 20 (44%), not significant (NS) patients with normal, indeterminate scans, and PE, respectively, had been re-admitted to hospital. Of these hospitalizations 15 (45%), 19 (61%), and 13 (65%), NS had been for heart failure or dyspnoea. The median improvement of a functional class was found in all three groups, $P_{0.0001}$ for all groups, with no differences between groups.

Age-adjusted mortality rate in patients with indeterminate V/Q scans at inclusion were significantly higher than in patients with normal V/Q scans or PE at 1 year follow-up, 16 vs. 12 or 10%, $P_{0.0004}$, with similar long-term trends, 41 vs. 20 or 23%, $P_{0.0001}$, respectively, Figure 2. When stratifying the population by PA acceleration time, a significantly higher age-adjusted mortality rates in patients with PA acceleration time $/C20$ was found, $P_{0.0001}$.

The predictive information from baseline echocardiographic parameters on long-term survival is shown in Table 1, showing that PA acceleration time, TAPSE, and LV ejection fraction were strongly associated with mortality in the univariate models, $P_{0.0001}$. No interaction with results of V/Q scans was identified, and in sub-group analysis by result of the V/Q scan similar trends were found, data not shown. A multivariate model showed that PA acceleration time and LV ejection fraction had incremental prognostic information, $P_{0.006}$ and 0.02, respectively, even when adjusted for the effect of age and sex, Table 1. To adjust for the impact of heart rate on PA acceleration time the analysis was repeated indexing the PA acceleration time to heart rate, and by including heart rate in the multivariate analysis. Both analyses yielded similar results as presented for the un-adjusted measure, data not shown.

When analysis in the sub-group of patients in whom no PE on V/Q scan was found, $N = 225$, the PA acceleration time was still predictive of mortality [HR (hazard ratio) = 0.79, $P < 0.0001$ per 10 ms increase].

Echocardiographic follow-up in patients with pulmonary embolism

Causes of death during the first year were cardiovascular in two cases, cancer in two patients and unknown in four patients. Forty-five (78%) patients of the 58 patients diagnosed with PE, completed the telephone interview, and 41 patients agreed to the follow-up echocardiography as two patients refused the echocardiography and two patients were unable to participate for medical reasons, Figure 1.

In univariate analysis in patients with PE an increased RV to LV diameter ratio, a reduced PA acceleration time, TAPSE or LV ejection fraction seemed predictive event-free survival within the first year after first non-massive PE. Only PA acceleration time and LV ejection fraction were independently related to event-free mortality, when adjusting for age and sex, Table 2. RV free wall mid-wall strain or other TDI-based parameters were not associated with all-cause mortality or event-free survival, data not shown. No differences in survival or event-free survival were found when stratifying the PE population by size of perfusion defects at the baseline echocardiography, data not shown.

On the echocardiographic 1 year follow-up, no changes in blood pressure, $136 \pm 26 / 83 \pm 16$ vs. $135 \pm 22 / 80 \pm 10$ mmHg, NS, or prevalence of peripheral oedema, 13 (22%) vs. 11 (21%), NS, were seen. The prevalence of negative T-waves in V1–V3 decreased significantly, 29 vs. 3% $P = 0.004$. Compared with baseline, PA acceleration time increased from $89 \pm 23$ to $116 \pm 31$ ms, $P < 0.0001$.
and measures of global RV systolic function (i.e. RV fractional shortening, RV outflow tract fractional shortening, and TAPSE) improved, Table 3. In Figure 3 the individual changes in echocardiographic parameters found to be predictive of outcome in the multivariate model are shown, illustrating a reduction in RV after-load and unchanged LV ejection fraction.

Discussion

In patients suspected of first non-massive PE, long-term survival is similar in patients in whom PE is confirmed and patients with normal V/Q scans, whereas patients with indeterminate V/Q scans carry a poorer prognosis. The PA acceleration time as a measure of RV after-load and LV ejection fraction hold significant prognostic information over the V/Q scan. At 1 year follow-up, the PA acceleration time and global RV systolic function are improved and normalized in patients with PE.

Changes in the pulmonary blood flow through the pulmonary valve have previously been shown to occur in pulmonary hypertension. A mid-systolic peak in outflow velocity is seen in mid-systole in patients with normal pulmonary resistance, and with increasing resistance, the blood accelerates rapidly to its peak earlier in systole, thereby shortening the time interval from onset to peak flow rate, i.e. PA acceleration time. An inverse log-linear relation of PA acceleration time and pulmonary pressures has been found, with the closest correlation with mean PA pressure as used for estimation of RV pressure in the present study.

Follow-up in patients referred for ventilation/perfusion scintigraphy

The present report consolidates earlier findings that the survival is similar in patients in whom PE is confirmed and patients in whom PE is excluded, and adds that the sub-group of patients where a definite diagnosis cannot be made by V/Q scan has a significantly worse prognosis and may thus be eligible for further evaluation. Indeterminate V/Q scans are more frequent in elderly patients and in patients with chronic obstructive pulmonary disease or emphysema, which may be a part of the reason for the increased mortality found in the present study. Chronic obstructive pulmonary disease was more prevalent in this group in the present study, but as baseline demographics and clinical finding were similar in the groups, the echocardiographic findings may still be relevant parameters for the assessment of risk in this heterogeneous group of patients.

Univariate analysis showed that several quantitative measures of RV pressure and global systolic function were related to mortality, whereas as the novel tissue Doppler based measures of regional RV myocardial function seem to be of minor importance in risk assessment. The multivariate survival analysis suggested that even though presence of PE is not a significant predictor of mortality, echocardiographic findings suggestive of increased RV after-load and LV heart failure are important risk factors in these patients. Other echocardiographic indices of global RV systolic function were also related to outcome, but PA acceleration time was the stronger predictor of mortality. Pulmonary hypertension in heart failure has also been shown to carry significant prognostic information. Both the TR gradient and the PA acceleration time have been shown to be measures of RV pressure, and the authors speculated that PA acceleration time may be the stronger predictor of mortality in part due this parameter being technically easy to obtain.

LV ejection fraction as an essential parameter in the use of echocardiography in patients admitted with dyspnoea is widely accepted, and the present study adds that this parameter, along with evaluation of RV overload is useful predictor of outcome in patients suspected of PE.
Outcome in patients with pulmonary embolism

The overall mortality in patients with PE found in the present study was similar to previous studies in patients with non-massive PE.22,27,28 RV dysfunction has been associated with adverse outcome in patients with PE,3,28,29 although other studies were unable to identify predictive echocardiographic factors,30,31 as found in the present study. However, acknowledging that the sample size for the sub-group analysis in this prospective study would limit the power of stratified analysis, we predefined a secondary end-point of heart failure related hospitalization and death. Several of the quantitative echocardiographic parameters of RV pressure and global function were found to be predictive of event-free 1 year survival, the PA acceleration time and LV ejection fraction were found to be the stronger predictors of outcome.

The novel tissue Doppler-based measures of myocardial deformation, previously shown to be reduced in PE patients,14 were not related to outcome, even though isolated mid-wall hypokinesis is thought to be a specific feature of larger PE.32 Obtaining imaging for evaluation of regional myocardial deformation and deformation rate is challenging, and a previous study has identified higher levels of variability than found in spectral Doppler and 2D-based imaging.33

Echocardiographic measures of RV overload, previously shown to be related not only to the presence of PE, but also to the extent of embolism, improved during the
1 year follow-up. TAPSE as a measure of global RV systolic function is related to the presence and extent of PE, and has recently been suggested as a sensitive marker of persisting RV dysfunction. Interestingly, longitudinal RV dysfunction may persist beyond the usual time for thrombi to resolve, whereas TR pressure gradient, a measure of RV systolic pressure, may be closely related to resolution of perfusion defects. The underlying mechanism remains to be established, but studies do suggest that follow-up evaluation of RV dysfunction 3–6 months of the diagnosis cannot exclude further recovery of function.

The PA acceleration time is shortened with RV pressure overload, and has been shown to be a diagnostic marker of PE, and in particular proximal thrombi. Interestingly, the PA acceleration time was the more predictive parameter in the multivariate analysis. If confirmed in future studies in patients suspected of non-massive PE, this parameter seems to be useful not only in the initial diagnostic work-up of these patients, but may also provide useful prognostic information.

Conclusions
Quantitative measures of global and regional RV function may add prognostic information in patients suspected of non-massive PE.

Table 3  Electrocardiographic and echocardiographic findings at baseline and after 1 year in patient diagnosed with pulmonary embolism, N = 41

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>Follow-up</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>ECG</strong></td>
<td></td>
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<tr>
<td>Normal sinus rhythm, n (%)</td>
<td>30 (86%)</td>
<td>31 (89%)</td>
<td>NS</td>
</tr>
<tr>
<td>Right bundle branch block, n (%)</td>
<td>6 (17%)</td>
<td>11 (31%)</td>
<td>NS</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>90 ± 17</td>
<td>93 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>S1S3TIII pattern, n (%)</td>
<td>6 (18%)</td>
<td>1 (3%)</td>
<td>NS, 0.06</td>
</tr>
<tr>
<td>Negative T-wave in V1-V2, n (%)</td>
<td>10 (29%)</td>
<td>1 (3%)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
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<tr>
<td>RV end-diastolic diameter (cm)</td>
<td>3.2 ± 0.7</td>
<td>3.2 ± 0.6</td>
<td>NS, 0.84</td>
</tr>
<tr>
<td>RV to LV diameter ratio</td>
<td>0.92 ± 0.31</td>
<td>0.80 ± 0.24</td>
<td>0.01</td>
</tr>
<tr>
<td>TR maximum pressure gradient (mmHg)</td>
<td>37 ± 14</td>
<td>31 ± 14</td>
<td>NS, 0.08</td>
</tr>
<tr>
<td>PA acceleration time (ms)</td>
<td>89 ± 23</td>
<td>116 ± 31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RV fractional shortening (%)</td>
<td>17 ± 8</td>
<td>26 ± 11</td>
<td>0.005</td>
</tr>
<tr>
<td>RV outflow tract fractional shortening (%)</td>
<td>32 ± 12</td>
<td>43 ± 12</td>
<td>0.0007</td>
</tr>
<tr>
<td>TAPSE (cm)</td>
<td>1.8 ± 0.4</td>
<td>2.0 ± 0.4</td>
<td>0.01</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>56 ± 7</td>
<td>55 ± 9</td>
<td>NS</td>
</tr>
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</table>

*ECG information available in 35 patients.

Figure 3 Changes in quantitative echocardiographic measures found to be predictive of outcome in the multivariate model (Table 2) in patients diagnosed with first non-massive pulmonary embolism compared with finding at 1 year follow-up. The pulmonary artery (PA) acceleration time, top panel (corresponding to a mean pulmonary pressure of 33 ± 12 mmHg at baseline and 23 ± 10 mmHg at follow-up) and left ventricular (LV) ejection fraction, bottom panel. Error bars represent mean ± SD for patients with measurements available at baseline and at follow-up. Filled circles represent patients dying within 1 year from baseline, P-value refers to changes from baseline to follow-up examination.

PA acceleration time, as a measure of RV after-load, adds incremental prognostic information on top of information of V/Q scan. Significant improvement in echocardiographic and electrocardiographic markers of RV dysfunction is seen at 1 year follow-up, and among measures of RV pressure and function, the PA acceleration time seems to be the stronger...
predictor of event-free survival in patients with confirmed PE.

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