Prognostic Value of Echocardiographically Assessed Right Ventricular Dysfunction in Patients With Pulmonary Embolism

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Background: Echocardiographically assessed right ventricular dysfunction is increasingly used to guide more aggressive therapy in hemodynamically stable patients with acute pulmonary embolism (PE). However, the prognostic value of right ventricular dysfunction in these patients is still unclear.

Methods: We systemically reviewed the literature to assess the prevalence of echocardiographic right ventricular dysfunction and the association with adverse outcomes in patients with PE who had this condition. The methodologic quality of each study was scored. Absolute risks of the outcome events were calculated for each study separately, and positive predictive values of PE-related mortality were determined for normotensive patients.

Results: Seven studies were included. All had methodologic shortcomings, but they suggested an at least 2-fold increased risk of PE-related mortality in patients with right ventricular dysfunction, the prevalence of which varied from 40% to 70%. However, this seems to be less convincing in hemodynamically stable patients. The only 2 studies that allowed for an estimation of the accuracy in normotensive patients showed low positive predictive values of echocardiographic right ventricular dysfunction for PE-related in-hospital mortality (positive predictive value, 4% and 5% in the 2 studies).

Conclusion: It remains unclear whether echocardiographic right ventricular dysfunction is a prevalent and reliable predictor of adverse outcomes in hemodynamically stable patients with acute PE.

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Before the introduction of anticoagulants, patients with pulmonary embolism (PE) had a poor prognosis. The chance of dying as a result of their disease was around 25%.1-3 Currently, hemodynamically stable patients with PE are routinely treated with a course of heparin and vitamin K antagonists as secondary prophylaxis, and the prognosis has considerably improved, with PE-related mortality rates ranging from 1.5% to 7%.4-7 To further reduce this rate, patients with a high risk of recurrent (fatal) PE could be treated more aggressively, ie, with thrombolytic agents or embolectomy. For the selection of these high-risk patients, a tool is needed that accurately predicts adverse outcomes at the time of presentation.

In 1993, Goldhaber and colleagues8 suggested a correlation between echocardiographic right ventricular dysfunction and poor outcome in patients with acute PE. They observed, in a randomized controlled trial of heparin vs thrombolysis, that all patients with recurrent PE, some of whom died, showed right ventricular hypokinesis on echocardiography. Since then, several studies have evaluated the importance of echocardiographic right ventricular dysfunction as a predictor of mortality, suggesting that 40% to 60% of unselected patients with PE may have echocardiographic right ventricular dysfunction.7,9-11 The majority of these patients were hemodynamically stable.

Recently, the first randomized, double-blind, placebo-controlled trial was published of thrombolyis and heparin vs heparin alone as initial treatment in patients with acute PE and concomitant pulmonary hypertension and/or (echocardiographic or electrocardiographic) right ventricular dysfunction.12 Remarkably, the in-hospital PE-related mortality was very low in both the thrombolysis and heparin only groups (1.7% and 1.4%, respectively) and, moreover, the prevalence of echocardiographic right ventricular dysfunction in this highly selected patient category was only 31%. This raises the ques-
tion of whether echocardiographically assessed right ventricular dysfunction is of clinical importance in hemodynamically stable patients with PE. We, therefore, performed a systematic review to establish whether echocardiographically assessed right ventricular dysfunction is a prevalent and reliable prognostic marker in patients with acute PE, in particular in those who are hemodynamically stable.

METHODS

LITERATURE SEARCH AND DATA SOURCES

Two reviewers (M.t.W. and E.Q.) searched the Ovid, MEDLINE, EMBASE, PubMed, Cochrane, and Web of Science databases, by combining the key words pulmonary embolism, right ventricular dysfunction, and echocardiography. Furthermore, abstracts were searched from the databases of relevant congresses. The same 2 reviewers independently selected trials suitable for inclusion in the analysis on the basis of the 3 criteria outlined in the following paragraph. For inclusion, all 3 criteria needed to be met. Disagreement between reviewers was resolved by discussion and consensus.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

1. Studies had to be prospective cohort studies or randomized controlled trials in patients with clinically suspected acute PE. Initial treatment had to be either heparin or thrombolysis, followed by vitamin K antagonists for a minimum of 3 months.

2. All patients with objectively proven PE had to undergo echocardiography to assess right ventricular function at baseline. Transthoracic echocardiography had to comprise assessment of right ventricular size, right ventricular wall motion by different views, pulmonary artery systolic pressure, tricuspid regurgitation, right ventricular wall thickness, or paradoxical septal movement.13,14

3. Patients needed to be clinically followed up for a minimum of 14 days or during the period of their in-hospital stay.

ANALYSIS

All studies were scored for their methodologic quality by evaluating the following criteria15: proper formation of an inception cohort (ie, were patients included consecutively and was the diagnosis of PE objectively confirmed by established methods?), description of referral pattern, completeness of follow-up, a priori definition of outcomes, blind outcome assessment, and adjustment for other prognostic factors.

Outcome measures were absolute risks of all-cause short-term mortality (ie, occurring within the in-hospital period or 14 days) and all-cause long-term mortality (defined by a minimum follow-up of 3 months) and mortality due to PE (short-term and long-term), in patients with and without right ventricular dysfunction. Positive predictive values were calculated in patients who were normotensive, since this was the population of interest. If no clinical or statistical heterogeneity was observed, pooled estimates of absolute risks of the outcome events were calculated.

RESULTS

The computer search yielded 62 references, of which 9 articles met our inclusion criteria.7-11,16-19 Two of these articles reported on previously published cohorts,10,17 hence these studies were excluded from further analysis.

METHODOLOGIC QUALITY OF THE STUDIES

Table 1 presents the results of the quality assessment of the 7 included studies.

In 3 studies it is unknown whether consecutive patients were included,8,10,18 whereas in 3 studies the diagnosis of PE was not always confirmed by established methods but by a suggestive echocardiogram and/or a high clinical suspicion of PE.7,10,19 Thus, only 2 studies had a proper inception cohort.

Most of the studies did not describe to which type of department (eg, coronary care unit) or type of hospital (eg, tertiary care clinic) patients were referred, making it difficult to analyze the referral pattern.

Follow-up was completed in all studies. Short-term follow-up was defined as the in-hospital period or an observation period of less than 14 days. The long-term follow-up varied among the studies from 3 months7 to longer than 6 months18 to 1 year9,10 or more.19

Apart from the study by Ribeiro et al.9 in none of the studies was it explicitly stated how the outcome criterion PE-related mortality was assessed and whether it was defined a priori. Moreover, none of the studies reported whether an independent committee, blinded to the cardiac status of the patient, assessed the outcome measurement.
Adjustment for other risk factors influencing mortality was not performed in the studies by Kasper et al and Jerjes-Sanchez et al. The other studies did evaluate the influence of extraneous prognostic factors. However, despite the fact that Goldhaber et al7 and Ribeiro et al9 did adjust for possible confounders by multivariate analyses, they did not control for treatment type, e.g., thrombolysis or placement of a caval filter.

**ECHOCARDIOGRAPHIC CRITERIA FOR RIGHT VENTRICULAR DYSFUNCTION**

In the majority of studies, right ventricular dysfunction was defined as right ventricular hypokinesis as assessed by a qualitative evaluation of the right ventricular wall motion.7-9,19 In the study by Kasper et al,10 right ventricular dysfunction was defined as follows: dilation of the right ventricular cavity (apical, subcostal, or transesophageal 4-chamber view) or right ventricular end-diastolic diameter greater than 30 mm (precordial view); or when 2 of the following items were satisfied: (1) tricuspid regurgitation velocity greater than 2.8 m/s, (2) tricuspid regurgitation velocity greater than 2.5 m/s in the absence of inspiratory collapse of the inferior vena cava, (3) dilation of the right pulmonary artery (>12 mm/m²), (4) right ventricular wall thickness greater than 5 mm, or (5) loss of inspiratory collapse of the inferior vena cava. Grifoni and colleagues18 considered acute right ventricular dysfunction to be present when 1 or more of the following criteria were met: right ventricular dilation (end-diastolic diameter >30 mm or right ventricular–left ventricular end-diastolic diameter ratio >1 in 4-chamber view); or paradoxical septal systolic movements or pulmonary hypertension (defined as Doppler pulmonary acceleration time <90 milliseconds or presence of a right ventricular-atrial gradient >30 mm Hg). In addition, right ventricular wall hypertrophy (free wall thickness, >7 mm) needed to be absent. Thus, among the different studies, no uniform criteria were used to assess the presence of right ventricular dysfunction.

**PATIENT CHARACTERISTICS**

Table 2 summarizes the baseline clinical characteristics and overall outcomes of the included studies. A large degree of heterogeneity was observed in the included patients with regard to their hemodynamic status. The percentage of patients receiving thrombolytic therapy varied from 100% in the study by Jerjes-Sanchez et al19 to 15% in the studies by Goldhaber et al,7 Grifoni et al,18 and Kasper et al.10 One fourth of the patients in the study by Ribeiro and colleagues8 received thrombolytic therapy, whereas half of the patients (by definition) in the randomized trial by Goldhaber et al8 received this treatment. Also, variation was observed in the proportion of included patients with objectively proved PE who underwent echocardiography, which varied from 46% to 100%. The prevalence of right ventricular dysfunction in patients with PE ranged from 40% to 70%. Finally, the studies varied with respect to their overall outcomes: short-term all-cause and PE-related mortality rates ranged from 2% to 13% and from 2% to 10%, respectively.

**RIGHT VENTRICULAR DYSFUNCTION AND OUTCOMES**

As a result of the observed heterogeneity of the included studies—with respect to their methodologic quality, the echocardiographic criteria of right ventricular dysfunction, and the patient characteristics—pooling of the results and performance of statistical analysis to obtain one overall estimate of the studied outcome measures were not meaningful. We will therefore describe the different studies separately.

Table 2 gives the outcomes of the included studies stratified for the presence or absence of right ven-

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Mean Age, y</th>
<th>Hemodynamic Status</th>
<th>Thrombolytic Treatment, No. (%)</th>
<th>Patients With Confirmed PE and Available Echocardiography, No.</th>
<th>Patients With RV D, No. (%)</th>
<th>Total Mortality, No. (%)</th>
<th>Mortality Due to PE, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldhaber et al7, 1993</td>
<td>101</td>
<td>59</td>
<td>Stable</td>
<td>46 (46)</td>
<td>NDA</td>
<td>2 (2)</td>
<td>NDA</td>
<td>NDA</td>
</tr>
<tr>
<td>Ribeiro et al3, 1997</td>
<td>157</td>
<td>&gt;65</td>
<td>Not reported</td>
<td>37 (24)</td>
<td>126</td>
<td>70 (56)</td>
<td>10 (8)</td>
<td>19 (15)</td>
</tr>
<tr>
<td>Kasper et al10, 1997</td>
<td>317</td>
<td>59</td>
<td>Not reported</td>
<td>49 (15)</td>
<td>164</td>
<td>72 (44)</td>
<td>29 (9)</td>
<td>30 (9)</td>
</tr>
<tr>
<td>Goldhaber et al3, 1999</td>
<td>2454</td>
<td>62</td>
<td>2182 Stable, 169</td>
<td>49 (15)</td>
<td>1135</td>
<td>454 (40)</td>
<td>280 (11)</td>
<td>426 (17)</td>
</tr>
<tr>
<td>Grifoni et al11, 2000</td>
<td>209</td>
<td>65</td>
<td>162 Normotensive, 19 Hypotensive, 28 Shock</td>
<td>31 (15)</td>
<td>207</td>
<td>110 (53)</td>
<td>17 (8)</td>
<td>NDA</td>
</tr>
<tr>
<td>Grifoni et al18, 2001</td>
<td>117</td>
<td>63</td>
<td>Not reported</td>
<td>NDA</td>
<td>117</td>
<td>48 (41)</td>
<td>NDA</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Jerjes-Sanchez et al19, 2001</td>
<td>40</td>
<td>47</td>
<td>Large/massive PE, 24 Normotensive</td>
<td>40 (100)</td>
<td>40</td>
<td>28 (70)</td>
<td>5 (13)</td>
<td>5 (13)</td>
</tr>
</tbody>
</table>

Abbreviations: NDA, no data available; PE, pulmonary embolism; RVD, right ventricular dysfunction.

*Follow-up during in-hospital period or less than 14 days.
tricular dysfunction. Six studies, including a total of 1773 patients, showed that patients with right ventricular dysfunction had at least a 2-fold higher risk of dying in the short term, as compared with patients without right ventricular dysfunction. The absolute difference ranged from 4% to 18%. This increase is supported by the multivariate analysis in the study by Ribeiro et al, which showed a relative risk of 6.0 (95% confidence interval, 1.1-11.5). The absolute differences in all-cause mortality rates between patients with and without right ventricular dysfunction remained higher after a longer duration of follow-up in most studies. The Goldhaber et al study and the study by Ribeiro and colleagues reported adjusted risk estimates for long-term total mortality; these multivariate analyses showed an odds ratio from 4% to 18% and 3% to 13%, respectively (Table 3). Only 2 studies allow for estimation in normotensive patients. In these studies, absolute differences with regard to short-term PE-related mortality were the lowest: 4% and 5%. In addition, the specificity and positive predictive value of right ventricular dysfunction for PE-related in-hospital mortality in hemodynamically stable patients were low (specificity, 61% and 56%; positive predictive value, 4% and 5%, respectively). Thus, the predictive potential of echocardiographic right ventricular dysfunction might be less reliable in hemodynamically stable patients.

The preceding conclusions have to be interpreted with great caution because they are based on studies with some potentially relevant methodologic shortcomings. (1) In the majority of studies it was not clear whether consecutive patients were included, how they were referred, or whether all patients definitely had PE. As a consequence, the risk of selection and referral bias cannot be excluded. This in particular may affect the prevalence of right ventricular dysfunction. (2) In none of the studies was it reported whether an independent blinded committee assessed the outcome criteria. Consequently, outcomes might be preferentially attributed to fatal PE because of diagnostic suspicion bias. (3) Most of the studies did not adjust for type of treatment or other important prognostic factors. Therefore, the risk

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**Table 3. Mortality in Patients With Pulmonary Embolism With and Without Right Ventricular Dysfunction**

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Total Mortality, No. (%)</th>
<th>Mortality Related to PE, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RVD Present</td>
<td>RVD Absent</td>
<td>RVD Present</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RVD Present</td>
</tr>
<tr>
<td>Goldhaber et al.³ 1993</td>
<td>46</td>
<td>2 (4)</td>
<td>NDA</td>
</tr>
<tr>
<td>Ribeiro et al.⁵ 1997</td>
<td>70</td>
<td>10 (14)</td>
<td>15 (21)</td>
</tr>
<tr>
<td>Kasper et al.⁶ 1998</td>
<td>NDA</td>
<td>NDA</td>
<td>NDA</td>
</tr>
<tr>
<td>Goldhaber et al.⁵ 1999</td>
<td>87</td>
<td>16 (18)</td>
<td>16 (18)</td>
</tr>
<tr>
<td>Grifoni et al.⁷ 2000</td>
<td>110 (65†)</td>
<td>14 (13)</td>
<td>NDA</td>
</tr>
<tr>
<td>Grifoni et al.⁸ 2001</td>
<td>48</td>
<td>69 (69)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Jerjes-Sanchez et al.⁹ 2001</td>
<td>28</td>
<td>12 (18)</td>
<td>5 (18)</td>
</tr>
</tbody>
</table>

Abbreviations: NDA, no data available; PE, pulmonary embolism; RVD, right ventricular dysfunction.

*Percentage estimated from the Kaplan-Meier curve.
†Normotensive patients.

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**COMMENT**

The prognosis of acute PE ranges from good—for which in special cases avoiding therapy might even be safer20—to a poor outcome despite aggressive treatment. A bad prognosis seems to be associated with the severity of hemodynamic impairment. In the Management Strategy and Prognosis in Pulmonary Embolism Trial (MAPPET) registry²² the rate of death due to PE in patients with cardiac arrest, cardiogenic shock, and arterial hypotension was 60%, 23%, and 14%, respectively. If this correlation between ventricular function and mortality is extrapolated to patients with subclinical hemodynamic impairment (eg, hemodynamically stable patients with right ventricular dysfunction), a higher rate of fatal PE would be expected in these patients as compared with those without such a dysfunction. The aim of this review was to assess the prevalence of echocardiographic right ventricular dysfunction and to evaluate the predictive potential for adverse outcomes in patients with acute PE who have this condition.

On the basis of the currently available literature, the prevalence of right ventricular dysfunction ranges from 40% in normotensive patients to 70% in patients with large PE. The short-term as well as long-term mortality related to PE seems higher in patients with right ventricular dysfunction than in those without it; absolute differences range from 4% to 14% and 3% to 13%, respectively (Table 3). Only 2 studies allow for estimation in normotensive patients. In these studies, absolute differences with regard to short-term PE-related mortality were the lowest: 4% and 5%. In addition, the specificity and positive predictive value of right ventricular dysfunction for PE-related in-hospital mortality in hemodynamically stable patients were low (specificity, 61% and 56%; positive predictive value, 4% and 5%, respectively). Thus, the predictive potential of echocardiographic right ventricular dysfunction might be less reliable in hemodynamically stable patients.

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exists that patients with right ventricular dysfunction preferentially received a treatment that is associated with fewer or possibly more adverse outcomes. (+) The results apply to a patient population, which is not clearly defined with regard to its hemodynamic status. This is relevant because there is consensus that patients with hemodynamically unstable PE should receive thrombolytic therapy, whereas the controversy centers on the question of lytic therapy in hemodynamically stable patients with right ventricular dysfunction.

At present, risk stratification is based on clinical signs and symptoms. In patients with hypotension and circulatory collapse, thrombolysis is the therapy of choice.25,26 Some experts advocate a broadening of the indication for thrombolytic therapy,25,26 whereas others believe that exposure to thrombolysis will result in unnecessary deaths and intracranial hemorrhage.27,28 Throughout the literature, many experts have called for a randomized trial of heparin vs thrombolysis in patients with PE and echocardiographic right ventricular dysfunction.20-31 Meanwhile, such a trial has been carried out, and no treatment difference was observed in clinically relevant outcomes such as recurrent fatal or nonfatal PE.12 As is evident from this review, no definitive data are available on the prognostic significance of echocardiographic right ventricular dysfunction in hemodynamically stable patients with PE. For this group, evidence is required because hemodynamically unstable patients already have an indication for more aggressive therapy. Therefore, one step back would be needed, i.e., a methodologically rigorous trial to conclusively answer the question regarding the prognostic significance of echocardiographic right ventricular dysfunction in hemodynamically stable patients with acute PE, before it can be advocated that these patients should be exposed to thrombolysis or other forms of more aggressive therapy. An additional requirement would be a uniformly accepted definition of the criteria for echocardiographically detected right ventricular dysfunction. At present, the variety in criteria hampers the proper evaluation of the prognostic significance.

In conclusion, the prognostic importance of right ventricular dysfunction in patients with acute PE remains unclear because most of the available studies are of insufficient methodologic quality. They suggest that right ventricular dysfunction predicts adverse outcomes; however, this predictive potential seems less strong in hemodynamically stable patients with acute PE. It needs to be convincingly shown that the risk of aggressive therapy outweighs the potentially small gain in absolute benefit, as measured by PE-related mortality.

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