The frequency of diagnosing acute pulmonary embolism (PE) in Japan has increased with the advances in diagnostic modalities, but mortality has increased significantly over the past decades. There are 2 groups of PE cases in terms of location of onset: in-hospital and out-of-hospital. Goldhaber et al described ‘primary’ PE as occurring outside of the hospital and without predisposing cancer, trauma, or surgery, whereas ‘secondary’ PE occurred during or soon after hospitalization and had predisposing factors. Other have reported that the division between in-hospital onset and out-of-hospital onset was equal. Most patients with in-hospital onset have one or more predisposing factors, but approximately 50% of patients with out-of-hospital onset do not have any documented predisposing factors. However, there has been a report regarding the differences in hemodynamics and outcome in terms of the location of onset, which was the aim of the present study.

**Methods**

We studied retrospectively 56 consecutive patients with acute massive or submassive PE who were admitted to the Intensive Care Unit in Nippon Medical School Hospital between May 1992 and October 2002. The definitions of massive and submassive PE followed the guideline of the European Society of Cardiology. Massive PE comprises shock or hypotension (defined as systolic blood pressure (SBP) less than 90 mmHg or a decrease of more than 40 mmHg over 15 min). A subgroup of patients with submassive PE can be identified by the echocardiographic finding of right ventricular dysfunction without hemodynamic instability. All patients except for one had confirmation of PE by pulmonary angiography, and the remaining patient had confirmation from a ventilation-perfusion lung scan performed after acute phase treatment.

Patients were divided into 2 groups in terms of the location of onset: Group A comprised patients with in-hospital onset and Group B was those with out-of-hospital onset. Patients in Group A (n=28) had more frequent comorbidities with hemodynamic instability (54% vs 4%, p<0.0001) and temporary risk factors (93% vs 11%, p<0.0001), whereas patients in Group B (n=28) had a longer duration of symptoms (median: 5.5 days vs 0.5 day; p<0.0001), and had higher systolic pulmonary artery pressure (63±17 mmHg vs 46±12 mmHg, p=0.0006). Although in-hospital mortality did not differ between the 2 groups, the recurrence rate was higher in Group B (23% vs 0%, p=0.03).

**Conclusions**

Patients who had in-hospital onset of PE had mostly temporary risk factors, unstable hemodynamics and a lower recurrence rate compared with the cases of out-of-hospital onset. In cases of in-hospital onset, prompt diagnosis and suitable treatment is needed to prevent fatalities and cases of out-of-hospital onset should be followed carefully for recurrence. (Circ J 2004; 68: 988–992)

**Key Words:** In-hospital onset; Out-of-hospital onset; Prognosis; Pulmonary embolism
Prognosis for APE According to Location of Onset

Management Strategies

Intravenous heparin was started as soon as PE was suspected with a bolus dose of 3,000–5,000 IU, followed by continuous infusion with 15,000–24,000 IU/day, later adjusted to maintain an activated partial thromboplastin time between 45 and 70 s. Semi-emergency pulmonary angiography with catheter interventional therapy was performed. Catheter-directed thrombolysis was the treatment in 1992–1997, but from 1998 it was aggressive catheter interventional therapy. 

Aggressive catheter interventional therapy is a combination of the following procedures: (1) catheter-directed thrombolysis: tissue-type plasminogen activator (tisokinase) is administered from the catheter tip, usually before and after embolus-fragmentation, and the highest dose was 6.4 million IU; (2) embolus fragmentation: using a 6Fr K-PA pigtail catheter (Medikit; Tokyo, Japan), which has a side-hole in the curvature of the pig-tail loop that allows passage of a guide wire, the pigtail is rotated manually over the fixed wire and simultaneously moved back and forth; (3) thrombectomy: aspiration of thrombus using a 8Fr percutaneous transluminal coronary angioplasty guiding catheter (Judkins right guide size 4) through a long sheath inserted into the main pulmonary artery; (4) temporary caval filter placement until the severity of deep vein thrombosis (DVT) was determined. All procedures were performed via a femoral vein. Continuous urokinase infusion was systemically started with 480,000 IU/day, followed by a dose adjusted to maintain fibrinogen levels between 150 and 200 mg/dl. The duration

Table 1 Clinical Characteristics of the Patients With Pulmonary Embolism

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>A: In-hospital onset (n=28)</th>
<th>B: Out-of-hospital onset (n=28)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57±14</td>
<td>60±16</td>
<td>0.43</td>
</tr>
<tr>
<td>Female</td>
<td>22 (79%)</td>
<td>16 (57%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Duration of symptoms (median, days)</td>
<td>0.5 (0–31)</td>
<td>5.5 (0–90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cancer</td>
<td>6 (21%)</td>
<td>2 (7%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Post-surgery</td>
<td>18 (64%)</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>4/26 (15%)</td>
<td>8/26 (31%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Temporary risk factor</td>
<td>26 (93%)</td>
<td>3 (11%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Permanent risk factor</td>
<td>7 (25%)</td>
<td>12 (43%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>21/26 (81%)</td>
<td>20/26 (77%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Hypotension</td>
<td>6 (21%)</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Shock</td>
<td>9 (32%)</td>
<td>1 (4%)</td>
<td>0.01</td>
</tr>
<tr>
<td>PCPS</td>
<td>4 (14%)</td>
<td>1 (4%)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Values given as no. (%) or mean±SD, unless otherwise indicated. PCPS, percutaneous cardiopulmonary support.

Fig 1. Comparison of the predisposing factors in Group A (in-hospital onset) and Group B (out-of-hospital onset). A temporary risk factor (open bars) was detected more frequently in Group A than Group B (93% vs 11%, p<0.0001). Patients with idiopathic origin (closed bars) were fewer in Group A than Group B (0% vs 42%, p<0.0001). There were no differences in a permanent risk factor between the groups (gray bars).
of infusion was determined by the amount of residual thrombus and the severity of DVT, evaluated by venography. In patients with a bleeding risk, the dose of a thrombolytic agent was adjusted at the attending physician’s discretion. After stabilization of their general condition, all patients began oral warfarin therapy for more than 6 months at an international normalized ratio of prothrombin time of 2.0–2.5.

Statistical Analysis
Analyses were performed with StatView software version 5.0 (SAS Institute Inc; Cary, NC, USA). Continuous variables were expressed as the mean±SD or median. The dichotomous variables were expressed as percentages. Statistical comparisons of continuous variables were performed by the Student’s t-test or Mann-Whitney’s U test, as appropriate. Statistical comparisons of dichotomous variables were performed by the chi-square test or Fisher’s exact test, as appropriate. All probability values were 2-tailed, and values of less than 0.05 were considered statistically significant.

Results
Clinical Characteristics (Table 1, Fig 1)
The study group consisted of 56 patients with acute massive or submassive PE of which 28 comprised Group A (in-hospital onset) and 28 were Group B (out-of-hospital onset). The duration of symptoms was shorter in Group A than Group B (0.5 vs 5.5 days (median), p<0.0001). The predisposing factors in Group A were recent major surgery (n=12), cancer (n=6), thrombophilia (n=4), immobilization (n=2), post coronary angiography (n=2), stroke (n=2), acute myocardial infarction, and burn. In Group B, thrombophilia (n=8), cancer (n=2), popliteal venous aneurysm (n=2), essential thrombocytosis, economy class syndrome, Crohn’s disease, and large myoma uteri were included as predisposing factors. A temporary risk factor was detected more frequently in Group A (93% vs 11%, p<0.0001). Patients with an idiopathic origin were fewer in Group A than Group B (0% vs 42%, p<0.0001). Thrombophilia was more frequent in Group B (31% vs 15%), but the difference was not statistically significant. Hemodynamic instability, such as shock or persistent hypotension, was more common in Group A (54% vs 4%, p<0.0001). There were no significant differences in age, gender, cancer or DVT between the 2 groups.

Hemodynamics and Arterial Blood Gas Analysis (Table 2)
The systemic SBP in Group A was significantly lower than in Group B (96±33 mmHg vs 130±21 mmHg, p<0.0001) and tachycardia was more pronounced in Group A (107±23 beats/min vs 94±13 beats/min, p=0.01). Systolic and mean PAP (sPAP and mPAP) in Group B were significantly higher than in Group A (63±17 mmHg vs 46±12 mmHg, p=0.0006 and 36±9 mmHg vs 29±9 mmHg, p=0.01). There were no differences in arterial blood gas analysis between the 2 groups.

Therapeutic Procedures and Effects (Table 3)
There were no differences in therapeutic procedures and the rate of reduction of sPAP. After procedures, sPAP and mPAP were higher in Group B than in Group A (45±15 mmHg vs 35±9 mmHg, p=0.01 and 27±6 mmHg vs 22±6 mmHg, p=0.08). Most thrombi obtained by thrombectomy indicated a histopathologically fresh thrombus with
abundant fibrin. An organizing thrombus was observed more frequently in Group B (42% vs 20%), but the difference was not statistically significant.

In-Hospital Mortality and Recurrence Rate (Table 4)

The median period of follow-up was 647 days (116–3,468 days). In-hospital mortality was higher in Group A (14% (n=4) vs 7% (n=2)), but the difference was not statistically significant. The causes of death were multiple organ failure (in 2 patients), cardiogenic shock with PE, and cancer. In Group B, 2 patients died from cardiogenic shock with PE. The recurrence rate was significantly higher in Group B (23% (n=6) vs 0%, p=0.03); 4 of 6 patients had a recurrence even under adequate anticoagulation and all of them had a propensity to recurrence (ie, a permanent risk factor or idiopathy). One patient had a recurrence during temporary cessation of warfarin during hospitalization for acute aortic dissection, and another had a recurrence during the exchanging of the temporary caval filter.

When comparing the prognosis of the patients with submassive PE to exclude the adverse influence of hemodynamic instability, the in-hospital mortality was similar between Group A and Group B (0% vs 3.7%), but the recurrence rate tended to be higher in Group B (23% vs 0%, p=0.08).

Discussion

The present study revealed differences in the clinical characteristics, hemodynamics and outcomes for in-hospital onset and out-of-hospital onset of acute massive and submassive PE.

Differences in the Clinical Characteristics

One classification defines ‘primary’ PE as out-of-hospital onset without predisposing cancer, trauma or surgery and ‘secondary’ PE as occurring during or soon after hospitalization, with predisposing factors. Past studies have shown that 99% of patients with in-hospital onset had one or more predisposing factors and approximately 50% of patients with out-of-hospital onset have documented predisposing factors. Our present results concur with those findings: 100% of the patients with in-hospital onset had predisposing factors, especially temporary risk factors, and only 50% of the patients with out-of-hospital onset had predisposing factors. Furthermore, most of the patients with out-of-hospital onset had either a permanent risk factor or unknown origin (idiopathy). In the study by Dote et al., one-third of the patients with PE had no definitive predisposing factors and all their patients had an out-of-hospital onset with insidious symptoms.

It has been reported that there is an equal proportion of cases according to location and this was found in the present study also. Heit et al. described hospitalization as an independent risk factor for venous thromboembolism (VTE) and the overall age- and sex-adjusted incidence of VTE was more than 100-fold higher among hospitalized patients compared with community residents.

Differences in Hemodynamics

Patients with in-hospital onset were prone to complicated hemodynamic instability and had a shorter duration of symptoms than patients with out-of-hospital onset. These findings suggest that in the case of in-hospital onset a massive thrombus flows into the pulmonary arteries, producing hemodynamic instability and although there may be a similar in patients with out-of-hospital onset, most of them probably die before they reach hospital. In fact, Kürkçiyen et al. reported that 55% of patients with cardiac arrest from PE had out-of-hospital onset.

Pulmonary artery pressure was significantly higher in patients with out-of-hospital onset: 40% had severe pulmonary hypertension with a mPAP > 40 mmHg. These patients also had a longer duration of symptoms than patients with in-hospital onset. Generally, mPAP never exceeds 40 mmHg in a typical case of acute onset so our findings might be explained by multiple small or moderately sized emboli flowing gradually into the pulmonary artery causing subacute onset that produced severe but adaptive pulmonary hypertension.

Differences in the Aspirated Thrombus

An organizing thrombus was observed more frequently in patients with out-of-hospital onset, which might be related to chronic DVT or delayed admission for PE. However, it was also identified in 20% of patients with in-hospital onset. In a histopathological study, Ro et al. reported that most cases of fatal PE contained both fresh and organized thrombus so clinicians must be aware of patients with a history of subclinical recurrence, which is less responsive thrombolysis, either in-hospital onset or out-of-hospital onset.

Differences in Prognosis

In the present study, patients with in-hospital onset had higher mortality, but not significantly, and a low recurrence rate, whereas patients with out-of-hospital onset had lower in mortality and a higher recurrence rate. These findings might result from the differences in hemodynamics and clinical characteristics. Patients with in-hospital onset might have fatal preconditions such as hemodynamic instability and less permanent risk factors. Most of the patients with out-of-hospital onset had stable hemodynamics, probably because those with instability died before reaching hospital, and had permanent risk factors or idiopathy. Generally, hemodynamic instability is related to death, and
the risk of recurrence is less in patients with a temporary risk factor than it is in those with permanent risk factor or idiopathic VTE. Sakama et al reported that the relative risk of PE mortality was elevated in males and the aged, but the present study did not find any differences between the 2 groups in terms of gender or age. The reason for the lack of a significant difference in mortality between the groups might related the treatment procedures in the present study. When limiting the comparison of prognosis to only patients with submassive PE, in order to exclude the adverse influence of hemodynamic instability, the recurrence rate tended to be higher in patients with out-of-hospital onset. Therefore, patients with out-of-hospital of PE should be thoroughly examined for permanent risk factors and should be carefully followed for recurrence, even while undergoing adequate anticoagulation therapy.

Study Limitations

This was a retrospective and single-center study, and contains a major potential source of bias. First, patients already in hospital will be treated more quickly than those who are out-of-hospital. Second, out-of-hospital onset patients with hemodynamic instability are more likely to die before they reach hospital and therefore any predisposing factors could not be fully assessed. These patients were not included in this study, although we investigated a realistic population seen in clinical practice. Third, there were no differences in the therapeutic procedures and the rate of reduction of PAP between the groups, but the catheter procedure changes annually and some of these changes might have affected the clinical course. Therefore, the results of this study require careful interpretation and whether they would be replicated in other countries would depend on the local barriers to access to health care, emergency response and availability of treatment for the management of PE, and other highly variable circumstances.

Conclusion

There were some differences in the clinical characteristics, hemodynamics, and outcomes between in-hospital onset and out-of-hospital onset of acute massive and submassive PE. Cases of in-hospital onset had unstable hemodynamics and a lower recurrence rate, whereas cases of out-of-hospital onset had a higher PAP and higher recurrence rate. In cases of in-hospital onset, prompt diagnosis and suitable treatment is needed in order to prevent fatalities and cases of out-of-hospital onset must be closely followed for recurrence.

References