Pulmonary Embolism is an Important Cause of Death in Young Adults

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Background  Population-based analysis shows that deaths from pulmonary embolism (PE) are increasing in the older age groups, but it is unclear to what degree PE contributes to death in different ages and gender.

Methods and Results  Potential contribution factors for all PE and for critical PE (in which PE was the primary cause of death or the main diagnosis) were examined in 396,982 autopsy cases. For all PE, odds ratio (OR) in males was 0.61 (95% confidence interval (CI) 0.59–0.64, \( p<0.0001 \)), compared with that in females. ORs were 1.10 (95% CI 1.05–1.14, \( p<0.0001 \)) in 1991–1994 and 1.19 (95% CI 1.14–1.25, \( p<0.0001 \)) in 1995–1998, compared with those in 1987–1990. ORs for ages 0–9 and 40+ were significantly low compared with that for ages 20–39. For critical PE, similar results were obtained. Pregnancy and/or delivery were found in 38.5% in cases of critical PE in females aged 20–39.

Conclusion  Compared with other age groups, PE contributed more to deaths in those aged 20–39 years. In recent years, deaths from PE have been slightly but significantly increasing. The incidence of clinically diagnosed critical PE also has been increasing.  \( \text{(Circ J 2007; 71: 1765–1770)} \)

Key Words:  Age; Delivery; Pregnancy; Pulmonary embolism

The number of deaths from pulmonary embolism (PE) has been increasing in Japan, and the incidence of PE in autopsy cases is also reported to have increased from 1958 to 1986. Population-based analysis shows that deaths from PE are increasing in older age groups but PE is often misdiagnosed.

There are no reports on the incidence of PE in autopsy cases after 1986 in Japan and the following remain to be solved: (1) to what degree does PE contribute to death in different ages and genders and (2) what factor(s) contributes to diagnosis of PE before death. Therefore, our aims in the present study were to examine the incidence of PE in autopsy cases after 1986, and to clarify these 2 unsolved questions.

Methods  The subjects of the present study included PE cases confirmed by autopsy in Japan between 1987 and 1998. We excluded cases of pulmonary microembolism with disseminated intravascular coagulation from our analysis.

\( \text{Circ J} 2007; 71: 1765–1770 \)

Key Words:  Age; Delivery; Pregnancy; Pulmonary embolism

Table 1  Embolic Source (n=11,367)

<table>
<thead>
<tr>
<th>Source</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombus</td>
<td>10,369 (91.2)</td>
</tr>
<tr>
<td>Tumor</td>
<td>503 (4.4)</td>
</tr>
<tr>
<td>Bacterial or fungal</td>
<td>247 (2.2)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>143 (1.3)</td>
</tr>
<tr>
<td>Fat</td>
<td>124 (1.1)</td>
</tr>
<tr>
<td>Amnionic fluid</td>
<td>49 (0.4)</td>
</tr>
<tr>
<td>Others*</td>
<td>25 (0.2)</td>
</tr>
</tbody>
</table>

Some cases had 2 or more sources.

*Air in 8 cases, cholesterin crystal in 6, contrast medium in 2, bone meal in 2 (both after bone fracture), foreign body in 2, and bile, amebic abscess, amyloid, ovum of parasite, and compression from the aorta in 1 case each.
A total of 11,367 PE cases (2.9%: 5,869 males, 5,474 females, and 24 cases without description of sex) were identified from 396,982 postmortem examinations (249,492 males, 146,484 females, and 1,006 cases without description of sex) between 1987 and 1998. We excluded cases without confirmation of the diagnosis. There were 4,363 cases of critical PE (2,097 males, 2,258 females, and 8 without description of sex). Cases of thrombotic PE accounted for 91% of all PE (Table 1). The age distribution of cases with all PE had a peak between 60 s and 70 s for both sexes (Fig 1). The ratio of all PE in autopsy cases by age, however, had a peak in young adults in both sexes (Fig 2). All PE, thrombotic PE, critical PE, and also clinically diagnosed critical PE increased (Tables 2, 3). Deep vein thrombosis (DVT) was reported in 1,044 (9.2%) cases among all PE.

As causes of critical PE according to patient age, heart diseases and major operations were prominent from birth to age 9, and almost all of the heart diseases were congenital. In this age group, there were no cases of critical PE diagnosed clinically. Cancer was a risk in many critical PE cases that were older than 10 years. In the 20s and 30s, pregnancy and/or delivery were associated with 38.5% of female cases with critical PE, whereas in males fractures and neuromuscular diseases were involved in 16% and 12.3% of cases, respectively (Table 4).

Table 2 Number of Cases of PE in Autopsies by Years

<table>
<thead>
<tr>
<th>Year</th>
<th>No. autopsies</th>
<th>All PE, n (%)</th>
<th>Thrombotic PE, n (%)</th>
<th>Critical PE, n (%)</th>
<th>Clinically diagnosed critical PE, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>39,399</td>
<td>1,169 (2.97)</td>
<td>1,063 (2.70)</td>
<td>336 (0.85)</td>
<td>46 (13.69)</td>
</tr>
<tr>
<td>1988</td>
<td>39,333</td>
<td>1,028 (2.61)</td>
<td>939 (2.39)</td>
<td>318 (0.81)</td>
<td>48 (15.09)</td>
</tr>
<tr>
<td>1989</td>
<td>38,459</td>
<td>972 (2.53)</td>
<td>895 (2.33)</td>
<td>299 (0.78)</td>
<td>44 (14.72)</td>
</tr>
<tr>
<td>1990</td>
<td>38,288</td>
<td>980 (2.56)</td>
<td>885 (2.31)</td>
<td>347 (0.91)</td>
<td>55 (15.85)</td>
</tr>
<tr>
<td>1991</td>
<td>36,474</td>
<td>1,141 (3.13)</td>
<td>1,047 (2.87)</td>
<td>430 (1.18)</td>
<td>71 (16.51)</td>
</tr>
<tr>
<td>1992</td>
<td>34,071</td>
<td>889 (2.61)</td>
<td>797 (2.34)</td>
<td>356 (1.04)</td>
<td>76 (21.35)</td>
</tr>
<tr>
<td>1993</td>
<td>31,949</td>
<td>1,030 (3.22)</td>
<td>946 (2.96)</td>
<td>419 (1.31)</td>
<td>72 (17.18)</td>
</tr>
<tr>
<td>1994</td>
<td>28,563</td>
<td>726 (2.54)</td>
<td>657 (2.30)</td>
<td>310 (1.09)</td>
<td>43 (13.87)</td>
</tr>
<tr>
<td>1995</td>
<td>28,602</td>
<td>899 (3.13)</td>
<td>813 (2.83)</td>
<td>426 (1.49)</td>
<td>81 (29.01)</td>
</tr>
<tr>
<td>1996</td>
<td>27,774</td>
<td>796 (2.87)</td>
<td>743 (2.68)</td>
<td>353 (1.27)</td>
<td>71 (20.11)</td>
</tr>
<tr>
<td>1997</td>
<td>27,391</td>
<td>857 (3.13)</td>
<td>781 (2.85)</td>
<td>370 (1.35)</td>
<td>81 (21.89)</td>
</tr>
<tr>
<td>1998</td>
<td>26,619</td>
<td>880 (3.31)</td>
<td>803 (3.02)</td>
<td>399 (1.50)</td>
<td>88 (22.06)</td>
</tr>
</tbody>
</table>

Numbers in parentheses show the percentage incidence in each year.
PE, pulmonary embolism.

Table 3 Univariate Analysis of Risk for PE in Autopsy Cases

<table>
<thead>
<tr>
<th>Year</th>
<th>All PE</th>
<th>Thrombotic PE</th>
<th>Critical PE</th>
<th>Clinically diagnosed critical PE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p value</td>
<td>OR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>1987–1990</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1991–1994</td>
<td>1.08 (1.04–1.13)</td>
<td>0.0004</td>
<td>1.08 (1.03–1.13)</td>
<td>0.001</td>
</tr>
<tr>
<td>1995–1998</td>
<td>1.16 (1.11–1.22)</td>
<td>&lt;0.0001</td>
<td>1.17 (1.11–1.23)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval. Other abbreviation see in Table 2.

Results

A total of 11,367 PE cases (2.9%: 5,869 males, 5,474 females, and 24 cases without description of sex) were identified from 396,982 postmortem examinations (249,492 males, 146,484 females, and 1,006 cases without description of sex) between 1987 and 1998. We excluded cases without confirmation of the diagnosis. There were 4,363 cases of critical PE (2,097 males, 2,258 females, and 8 without description of sex). Cases of thrombotic PE accounted for 91% of all PE (Table 1). The age distribution of cases with all PE had a peak between 60s and 70s for both sexes (Fig 1). The ratio of all PE in autopsy cases by age, however, had a peak in young adults in both sexes (Fig 2). All
Both all PE and critical PE occurred at low OR in males, including those under the age of 10 years or older than 39 years (Table 5). In the 20–39 years age group, critical PE was found in 2.3% of autopsy cases. ORs of thrombotic PE were 1.08 (95% CI 1.03–1.13; p=0.001) between 1991 and 1994, and 1.17 (95% CI 1.11–1.23; p<0.0001) between 1995 and 1998, when using the data between 1987 and 1990 as the reference. By similar analysis, ORs of critical PE were 1.16 (95% CI 0.97–1.40; p=0.11) between 1991 and 1994, and 1.40 (95% CI 1.17–1.67; p=0.0003) between 1995 and 1998. Both all PE and critical PE according to Mieno’s criteria increased year by year (Table 6).

Critical PE was diagnosed more frequently in the presence of DVT, recent major surgery, and more recent cases. On the other hand, it was less frequent in males and in the presence of cancer, heart diseases, chronic respiratory failure, neuromuscular diseases, and connective tissue diseases (Table 7).

Discussion

**PE in Young Adults**

Population-based analysis has shown that deaths from PE are increasing in older age groups and the present study results supports this finding. But from the viewpoint of incidence in deaths, PE contributed more to deaths in patients between the ages of 20–39 years than in other age groups. The number of deaths was less in this age group than in older age, but PE was more important as the cause of death. As the cause of natural death in the forensic setting, PE comprised 5.0% of the leading causes of death for ages 18–40; that is, higher than in the 41–60-years age group but PE was more important as the cause of death in older age groups. The number of deaths was less in this age group than in other age groups of males.

One main reason why the ratio of deaths from PE is higher in the 20–39 years age group compared with other ages is that the overall number of deaths in that cohort is low. Another reason is that there are many cases of PE in females resulting from pregnancy/delivery, which are well-known risk factors for PE. The number of PE reported in females resulting from pregnancy/delivery, which are well-known risk factors for PE, is 0.02% of total deliveries, 0.003% of vaginal deliveries, and 0.06% of cesarean deliveries between 1991 and 2000.

In Japan, the incidence in the fields of gynecology and obstetrics increased 6.5-fold in 2000 compared with 1991. In Japan, the incidence in obstetrics consists of 0.02% of total deliveries, 0.003% of vaginal deliveries, and 0.06% of cesarean deliveries between 1991 and 2000. The number of deaths was less in this age group than in older age groups of males.

**PE in Children Aged 0–9**

Although pediatric cases of PE are rare, it is suggested that the risk of venous thromboembolism increases when central venous catheters are used. The present study revealed that fatal PE was not diagnosed clinically in the 0–9 age group and the results indicate that even in children it is necessary to pay proper attention to the occurrence of PE associated with congenital heart diseases or major operations. Autopsy studies in Western countries have shown an incidence of PE ranging between 0.05% and 4.2% in childhood. The Canadian Registry of Venous Thromboembolism (VTE) indicated that the incidence of VTE in children (ages 1 month to 18 years) was 53/10,000 hospital admis-

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**Table 4 Characteristics in Autopsy Cases With Critical PE**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–9</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>10–19</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
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<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>20–39</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>40–59</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>60–70</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>80–</td>
<td>20</td>
<td>18</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

**Abbreviation see in Table 2.**
Incidence of PE

The present study showed that deaths from PE confirmed in autopsy have slightly but significantly increased in Japan, which is consistent with the results from death certificates1 and in clinical settings29–31. Improvement in diagnostic techniques, incremental increase of the geriatric population, and westernization of life style are suggested as factors causing the increase of PE in Japan29–31.

The changes in the incidence of autopsy-proven PE by year differ among countries. An autopsy study from Hong Kong documented a rising trend of PE from 1975 to 1989.32,33 Conversely, the incidence of PE in autopsies reduced in the United States from 1966 to 1980,34 and in the United Kingdom from 1965 to 2000, 35,36 but a Swedish study indicated that the incidence of PE was unchanged from 1957 to 1987.37 These differences may be related to differences in clinically diagnostic accuracy, in population structure, in prophylaxis and management of DVT/PE, and in life style.

Rate of Diagnosis of PE

We indicate that the incidence of clinically diagnosed critical PE is increasing, but it was only 22% in 1998. Walden et al showed that, in 425 autopsy cases with PE, 14% was diagnosed before death, 30% was written first on the death certificate, and 56% was revealed in autopsy.4 Another report indicated that, in 92 cases confirmed as PE by autopsy, 49% was considered as PE before autopsy and the remaining 51% was diagnosed by autopsy. Moreover, PE was assigned as the cause of death on the death certificate or in the medical report in 32% of 92 cases.38,39

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PE was diagnosed before death more accurately in the presence of DVT, recent major operation, and more recent cases, but was difficult to diagnose in association with collagen diseases, cancer, heart diseases, neuromuscular diseases, chronic respiratory failure, and in males. This finding partly confirms the finding that diagnosis of PE delayed in clinical cases, as we previously reported, when cardiac disease or pulmonary diseases exist.\(^{11}\)

**Study Limitations**

We could not sufficiently analyze the incidence of DVT in cases with PE. Generally, DVT is found in many cases of PE. DVT was detected in 165 legs (95%) among 174 cases with PE. Generally, DVT is found in many cases of PE in autopsy cases.\(^{41}\) However, in the present study, DVT was found in only 9.2% of cases with PE. The discrepancy between the previous reports and the present study may be related to insufficient examination for DVT in routine autopsy.

**Conclusion**

Compared with other ages, PE contributed more to deaths in those aged 20–39 years. In recent years, deaths from PE have been slightly but significantly increasing in Japan. The incidence of clinically diagnosed critical PE has also been increasing.

**Acknowledgment**

This study was partly supported by a grant from the Respiratory Failure Research Group from the Ministry of Health, Labour and Welfare, Japan.

**References**
