

# Incidence of pulmonary thromboembolism, infarction and haemorrhage in disseminated intravascular coagulation: a necroscopic analysis

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## Abstract

**Background** – The pathological features of the lung in disseminated intravascular coagulation (DIC) have not been established. This study was carried out on lungs taken at necropsy to examine the incidence and extent of thromboembolism, infarction, and haemorrhage.

**Methods** – The subjects were 87 patients whose illnesses were complicated by DIC and 64 patients who showed no abnormalities of blood coagulation in their terminal illness. The lungs were fixed by intrabronchial infusion of 10% formalin, cut into 5 mm thick slices, and each cut surface was carefully examined for macroscopic thromboembolism, infarction, and haemorrhage. Five tissue blocks per case were taken for quantitative analysis of microscopic thromboembolism.

**Results** – In the control group macroscopic thromboembolism was identified in 20 cases (31.3%), infarction in one, and haemorrhage also in one. Moreover, fibrin thrombosis was seen in 13 cases (20.3%) and microthromboembolism in 24 (37.5%). Of the 87 patients with DIC, thromboembolism was found in 51 cases (58.6%), infarction in six, haemorrhage in 14, microscopic fibrin thrombosis in 43 (49.4%), and microthromboembolism in 45 (51.7%). Macroscopic thromboembolism, haemorrhage, and fibrin thrombosis were found more often in the patients with DIC.

**Conclusions** – In addition to fibrin thrombosis, macroscopic thromboembolism and haemorrhage were the main pathological findings in the lungs of patients dying with DIC. The frequency of pulmonary infarction increased in proportion to the frequency of thromboembolism.

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Keywords: disseminated intravascular coagulation, pulmonary embolism, infarction, haemorrhage.

Previous studies<sup>1-3</sup> have shown that in patients with disseminated intravascular coagulation (DIC) pulmonary function frequently deteriorates, but the pathological background has not been established. Systemic thrombosis and haemorrhage occur with DIC as a result of the activation and consumption of clotting factors;<sup>4</sup> the possible pathological changes in the lung are fibrin thrombosis and haemorrhage.<sup>5-7</sup>

Robboy *et al*<sup>6</sup> and a previous study by our group<sup>8</sup> suggested a relationship between DIC and macroscopic thromboembolism. Case-control studies with adequate numbers are necessary to estimate such a relationship, as pulmonary thromboembolism is found in a high proportion of lungs when they are carefully examined at necropsy.<sup>9,10</sup> Furthermore, our earlier study<sup>8</sup> suggested the frequent occurrence of pulmonary infarction in DIC. Knowledge of the incidence and extent of haemorrhage, thromboembolism, and infarction may help in the management of patients with these pulmonary complications. It may also provide information about the mechanism of pulmonary dysfunction in DIC.

The purpose of this study was to establish the incidence of pulmonary thromboembolism, infarction, and haemorrhage at necropsy of patients who had died with the complications of DIC, and to examine the relationships between DIC and the pathological findings.

## Methods

### SUBJECTS

Of 741 necropsies performed between 1989 and 1992 in the Department of Pathology, Tokyo Metropolitan Geriatric Hospital, 87 cases were clinically diagnosed as being complicated by DIC. The diagnosis of DIC was made according to the criteria established by the Japanese Ministry of Health and Welfare.<sup>11</sup> The major features of this scoring system were prothrombin time (>15 seconds), fibrinogen concentration (<150 mg/dl), fibrin degradation products (FDP, >10 µg/ml), and platelet count (<12 × 10<sup>4</sup>/µl). Sixty four control cases were selected from the same series. The criteria for selecting the control subjects were no abnormalities in any of the following three coagulation tests performed within two days before death: prothrombin time (10.5–12.3 seconds), fibrinogen concentration (182–218 mg/dl), and platelet count (13–32 × 10<sup>4</sup>/µl). The clinical data were reviewed in relation to the diagnosis, triggers of DIC, duration of hospital stay, entry into the intensive care unit (ICU) or coronary care unit (CCU), chest radiographs, and respiratory problems.

### MACROSCOPICAL EXAMINATION

At necropsy both lungs were distended and fixed by intrabronchial infusion of 10% formalin with a constant pressure of 30 cm H<sub>2</sub>O. They were cut coronally into 5 mm thick slices,

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Table 1 Major diagnosis in the patients with disseminated intravascular coagulation (DIC) and in the control group

	DIC		Control	
	No	(%)	No	(%)
Malignancy	41	(47.1)	27	(42.2)
Infection	19	(21.8)	7	(10.9)
Cardiovascular disorder	10	(11.5)	11	(17.2)
Cerebral vascular disorder	6	(6.9)	9	(14.1)
Cirrhosis	4	(4.6)	0	(0)
Diabetes mellitus	2	(2.3)	3	(4.7)
Others	5	(5.8)	7	(10.9)
Total	87	(100)	64	(100)

DIC = disseminated intravascular coagulation.

Table 2 Incidence of pulmonary thromboembolism, infarction, and haemorrhage in the two study groups

	DIC		Control	
	No	(%)	No	(%)
Thromboembolism	51	(58.6)	20	(31.3)
Infarction	6	(6.9)	1	(1.6)
Haemorrhage	14	(16.1)	1	(1.6)
Fibrin thrombosis	43	(49.4)	13	(20.3)
Microthromboembolism	45	(51.7)	24	(37.5)

DIC = disseminated intravascular coagulation.

Table 3 Cumulative number of cases with the most proximally located thromboembolus

	DIC		Control	
	Cumulative no. of cases	(%)	Cumulative no. of cases	(%)
Interlobar artery	4	(7.8)	1	(5.0)
Lobar artery	6	(11.8)	1	(5.0)
Segmental artery	24	(47.1)	10	(50.0)
Subsegmental artery	46	(90.2)	17	(85.0)
Distal to subsegmental artery	51	(100)	20	(100)

DIC = disseminated intravascular coagulation.

and each cut surface was carefully examined for the presence of pulmonary thromboembolism, infarction, and haemorrhage.<sup>8</sup> In thromboembolism the dimension and external diameter of every occluded pulmonary artery<sup>12</sup> and the number of thromboemboli found in each case were recorded. Fibrous bands or webs were also included.<sup>13</sup> When thromboembolism was suspected the tissue block was taken and examined microscopically<sup>8</sup> to exclude the presence of blood clots, bone marrow emboli, tumour emboli, septic emboli, or fat emboli. For every infarct the segmental location,<sup>14</sup> greatest diameter, and external diameter of the occluded artery were recorded. Tissue blocks were taken from every infarcted area to confirm haemorrhagic necrosis distal to the thromboembolised artery and to estimate the healing stage. In pulmonary haemorrhage the number of segments involved was also recorded.

#### MICROSCOPICAL EXAMINATION

Apart from the tissue blocks taken above, five tissue blocks measuring approximately 2.5 × 4.5 × 0.8 cm were taken, one from each lobe, for microscopical examination. Fibrin thrombi and microthromboemboli were counted separately in all tissue sections.

#### DATA ANALYSIS

Analyses of the relationships between DIC and

the incidence of both macroscopic and microscopic thromboembolism, infarction, and haemorrhage were performed using Fisher's exact test or the  $\chi^2$  test. The difference in the number of cases who entered ICU or CCU between the two groups was also analysed with the  $\chi^2$  test. Comparisons of the duration of the hospital stay, the diameter of the thromboembolised artery, and the distribution of the number of thromboemboli between the two groups were made with the Wilcoxon rank sum test. All analyses were two sided and a p value of <0.05 was taken to be statistically significant.

#### Results

The mean (SD) age of the group with DIC was 80.2 (8.86) years (45 men) and that of the control subjects was 80.7 (9.33) years (36 men). The mean (SD) length of stay in hospital was 52.9 (68.5) days in the group with DIC and 37.8 (38.7) days in the control group. Fifteen subjects with DIC and six controls entered ICU or CCU. No significant difference was observed between the two groups in age, duration of hospital stay, and number in ICU or CCU. The major diagnoses are shown in table 1. The triggers for DIC were: sepsis or severe infection in 39 (44.8%), malignancy in 25 (28.8%), shock other than septic in 11 (12.6%), and others in 12 (13.8%).

#### THROMBOEMBOLISM

Macroscopic thromboemboli were found in 51 of the 87 cases with DIC (58.6%) and in 20 of the 64 control subjects (31.3%) ( $p < 0.01$ , table 2). When five cases in the DIC group with only fibrous bands or webs were excluded, the incidence still differed significantly. No patient from either group was diagnosed as having thromboemboli during life.

A total of 123 thromboemboli were found in the group with DIC and 38 in the control group. The most proximally located thromboemboli in both groups were in the interlobar arteries (table 3). Twenty four cases with DIC had thromboemboli in the segmental or more central arteries. Amongst them, six had thromboemboli in the lobar or interlobar arteries, including one with thromboemboli in bilateral interlobar arteries. Five of these six patients had tachypnoea, dyspnoea, or hypoxia; three had heart failure or pneumonia while the remaining two had no obvious pulmonary or cardiac complications.

The external diameter of the thromboembolised artery ranged from 1 to 9 mm, with the most common diameter being 2–3 mm (fig 1). There was no significant difference between the two groups in the external diameter or dimensional distribution of the thromboembolised arteries (fig 1, table 3). The number of thromboemboli per case is shown in fig 2. Again no significant difference was found between the two groups. In the control subjects no case had more than five thromboemboli, whereas in those with DIC two had 13 and 15 thromboemboli; one case had pancreatic cancer complicated by biliary tract infection and the other had acute suppurative cholangitis.

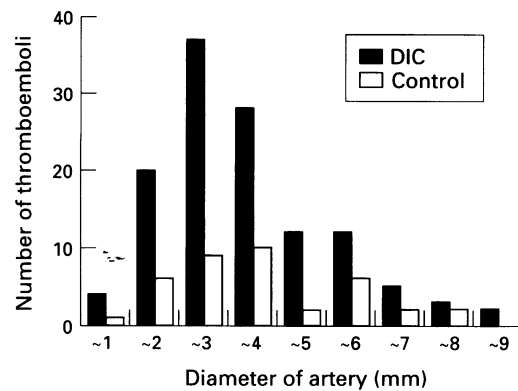


Figure 1 Distribution of the external diameter of the thromboembolised arteries in patients with disseminated intravascular coagulation (DIC) and control subjects. The external diameter was measured at the proximal portion of the thromboemboli.

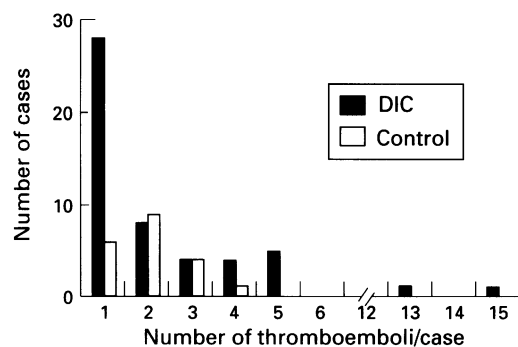


Figure 2 Distribution of the number of thromboemboli found in each case. A total number of thromboemboli per case was examined by cutting bilaterally inflated lungs into 5 mm thick slices. DIC = disseminated intravascular coagulation.

On microscopical examination, fibrin thrombi, which appeared as dense, homogeneous, and hyaline masses, were present in 43 of the subjects with DIC and in 13 of the 64 control cases (table 2). Microthromboemboli were morphologically similar to macroscopic thromboemboli and comprised both red and white blood cells in tangled fibrin aggregates. They were present in 45 cases with DIC and in 24 control cases. The incidence of fibrin thrombi was significantly higher in the group with DIC ( $p < 0.01$ ), whereas there was no difference in the incidence of microthromboemboli between the two groups. The numbers of fibrin thrombi and microthromboemboli/20 cm<sup>2</sup> of the microscopical sections in each positive case are shown in fig 3. There was no significant difference between

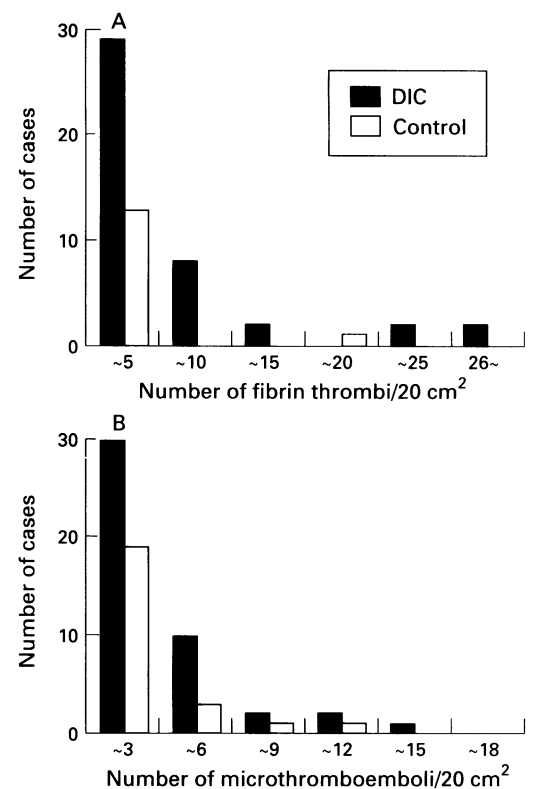


Figure 3 Distribution of the number of (A) fibrin thrombi and (B) microthromboemboli/20 cm<sup>2</sup> in the microscopical sections of the disseminated intravascular coagulation (DIC) and control groups.

the two groups in the number of fibrin thrombi or microthromboemboli. Two cases with DIC had more than 70 fibrin thrombi/20 cm<sup>2</sup>, one of whom had severe hypoxia without other pulmonary or cardiac complications before death.

#### INFARCTION

Pulmonary infarcts were seen in six cases with DIC and in one control subject (NS, table 2). All but one of the infarcts were in the lower lobes (table 4), and all were complete and recent. The diameters of the infarcts were all less than 60 mm. The rate at which thromboemboli were accompanied by infarcts was 4.9% in the group with DIC and 2.6% in the control group.

#### HAEMORRHAGE

Pulmonary haemorrhage was found in 14 of the 87 cases with DIC (16.1%) and in one of the 64 control subjects ( $p < 0.01$ , table 2). Apart from DIC, no case had a haematological disorder which caused a haemorrhagic diathesis or post chemotherapeutic bone marrow suppression severe enough to induce bleeding. In the cases with DIC the numbers of segments involved were one in 10 cases and two or three in four. In the latter cases alveolar densities on the chest radiographs and sudden respiratory failure were observed just before death. Necroscopic examinations revealed these densities to be from pulmonary haemorrhage. The one case in the control group who had recurrent episodes of myocardial infarction and severe

Table 4 Locations and sizes of the occluded arteries in cases with pulmonary infarcts

No	DIC (+/-)	Age/sex	Major diagnosis	Pulmonary infarction		
				Location	Greatest diameter (mm)	External diameter of occluded artery (mm)
1	+	93/F	CVD	R, S10	30	2
2	+	88/M	Colon cancer	R, S6	45	2
3	+	88/F	MI	R, S6	37	5
4	+	59/M	Gastric cancer	L, S3	16	1
5	+	79/F	Diabetes mellitus	R, S10	60	4
6	+	89/M	Lung cancer	R, S10	35	5
7	-	82/M	CVD	R, S6	30	1

DIC = disseminated intravascular coagulation; CVD = cerebral vascular disorder; MI = myocardial infarction; R = right; L = left; S = segment.

terminal congestive heart failure had massive pulmonary haemorrhage involving eight segments.

### Discussion

DIC is a pathological process in which activation of the coagulation system and consumption of clotting factors result in fibrin formation in the systemic circulation and haemorrhage in multiple organs including the lung. Previous studies of DIC<sup>3-8</sup> have revealed fibrin thrombi in the small pulmonary vessels and pulmonary haemorrhage, although little quantitative information on their incidence or extent. Previous studies by Robboy *et al*<sup>6</sup> and our group<sup>8</sup> have suggested a relationship between DIC and macroscopic thromboembolism and infarction. The present study showed that fibrin thrombosis, pulmonary haemorrhage and macroscopic thromboembolism occurred more frequently in patients with DIC than in a control group. There was also a tendency for infarction to be more frequent in cases with DIC (table 2).

Although it has received little emphasis, DIC is also a risk factor for macroscopic thromboembolism as well as microscopic fibrin thrombosis.<sup>15-17</sup> A 58.6% incidence of thromboembolism in DIC in the present study was comparable to our previous report<sup>8</sup> in which it occurred in 15 of 33 subjects with DIC. The high incidence of thromboembolism in the group with DIC is unlikely to be due to the longer hospital stay because this duration or admission to the ICU or CCU was similar in the two groups.

Since only a small number (five out of 51 cases) of the patients with DIC and thromboemboli had fibrous bands or webs, it can be assumed that most of the thromboemboli found in the present study were formed during the terminal period of illness. No patient was diagnosed as having thromboemboli during life.

The incidence of fibrin thrombi in the group with DIC was similar to that reported in the study of Kim *et al*<sup>7</sup> where pulmonary fibrin thrombi were found in 13 of 21 cases of DIC. Although the presence of fibrin thrombi has been considered pathognomonic of DIC,<sup>6</sup> they were also found in 13 of the control subjects. In these cases DIC may have occurred within the period between the final coagulation test and death.

The present quantitative study showed that the number of thromboemboli varied greatly among subjects with DIC (figs 2 and 3). Two subjects had more than 13 thromboemboli on macroscopical examination and two others had more than 70 fibrin thrombi/20 cm<sup>2</sup> in the microscopical sections. The actual number of thromboemboli formed during the episode of DIC may have been greater because most thromboemboli are known to undergo lysis or become incorporated into the vessel wall within 4-6 weeks.<sup>18</sup> Tomashefski *et al*<sup>19</sup> showed that in adult respiratory distress syndrome both macrothrombi and microthrombi were most numerous in the early stages, suggesting their lysis in the course of the syndrome.

It was impossible to distinguish morphologically between thrombi formed in situ and emboli. The origin of thromboemboli in DIC is controversial. Blaisdell *et al*<sup>20,21</sup> postulated that, in local injuries, intravascular coagulation and thrombosis would occur in the injured organs resulting in pulmonary embolism. On the other hand, in acute respiratory failure Schneider *et al*<sup>22</sup> reported that platelet sequestration occurred in the lung, and Rodvien *et al*<sup>23</sup> detected pulmonary sequestration of fibrinogen, suggesting in situ pulmonary thrombosis. In DIC, which is a systemic disorder, intravascular coagulation occurs in systemic organs including the lung, irrespective of triggers. It could be assumed therefore that pulmonary thromboemboli comprise both emboli from thrombi in the venous circulation and in situ thrombi formed in the pulmonary circulation.

The number of infarcts found in this study was small, and the incidence was similar to our previous study<sup>8</sup> in which infarcts were present in three out of 135 non-DIC subjects and four out of 33 subjects with DIC. All of the seven infarcts were of recent phase and could be considered to have occurred during the episode of DIC. The incidence of infarction was greater in the group with DIC than in the control group, but the ratio of thromboembolism accompanied by infarction was similar between the two groups, suggesting that DIC per se does not contribute to the development of infarction by an individual thromboembolus.

Multiple organ haemorrhages including the lung have been reported in DIC.<sup>5-7</sup> The incidence of pulmonary haemorrhage varies greatly: in seven out of 10 patients with DIC pulmonary haemorrhage was the direct cause of death,<sup>5</sup> whereas no haemorrhage was seen in 21 necroscopic cases of DIC.<sup>7</sup> The present study found pulmonary haemorrhage in 16.1% of the group with DIC, an incidence significantly higher than in the control subjects. Most of the haemorrhagic areas were small and rarely involved more than one segment. Abnormal alveolar densities on the chest radiograph newly formed during the DIC episode are usually considered to be inflammatory,<sup>5</sup> but this study suggested that some may be due to haemorrhage.

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- Fourrier F, Chopin C, Goudemand J, Hendrycx S, Caron C, Rime A, *et al*. Septic shock, multiple organ failure, and disseminated intravascular coagulation. *Chest* 1992;101:816-23.
- Bagge L, Haglund O, Wallin R, Borg T, Modig J. Difference in coagulation and fibrinolysis after traumatic and septic shock in man. *Scand J Clin Lab Invest* 1989;49:63-72.
- Bone RC, Francis PB, Pierce AK. Intravascular coagulation associated with the adult respiratory distress syndrome. *Am J Med* 1976;61:585-9.
- Colman RW, Robboy SJ, Minna JD. Disseminated intravascular coagulation (DIC): an approach. *Am J Med* 1972;52:679-89.
- Robboy SJ, Minna JD, Colman RW, Birmdorf NI, Lopas H. Pulmonary haemorrhage syndrome as a manifestation of disseminated intravascular coagulation: analysis of ten cases. *Chest* 1973;63:718-21.
- Robboy SJ, Major MC, Colman RW, Minna JD. Pathology of disseminated intravascular coagulation (DIC). Analysis of 26 cases. *Hum Pathol* 1972;3:327-43.

- 7 Kim H, Suzuki M, Lie JT, Titus JL. Clinically unsuspected disseminated intravascular coagulation (DIC). An autopsy survey. *Am J Clin Pathol* 1976;66:31-9.
- 8 Katsumura Y, Ohtsubo K, Saiki S, Noguchi E. Pulmonary thromboembolism and its clinical predisposing factors in autopsy cases. *Showa Univ J Med Sci* 1993;5:13-25.
- 9 Freiman DG, Suyemoto J, Wessler S. Frequency of pulmonary thromboembolism in man. *N Engl J Med* 1965; 272:1278-80.
- 10 Morrell MT, Dunnill MS. The post-mortem incidence of pulmonary embolism in a hospital population. *Br J Surg* 1968;55:347-52.
- 11 Kobayashi N, Maekawa T, Takada M, Tanaka H, Gonmori H. Criteria for diagnosis of DIC based on the analysis of clinical and laboratory findings in 345 DIC patients collected by the research committee on DIC in Japan. *Bibl Haematol* 1987;49:265-75.
- 12 Fraser RG, Paré JAP. Anatomy of the airways. In: Manke D, eds. *Diagnosis of disease of the chest*. 3rd ed, Vol 1. Philadelphia: Saunders, 1991:3-36.
- 13 Korn D, Gore I, Blenke A, Collins DP. Pulmonary arterial bands and webs: an unrecognized manifestation of organized pulmonary emboli. *Am J Pathol* 1962;40: 129-51.
- 14 Boyden EA. *Segmental anatomy of the lungs*. New York: McGraw-Hill, 1955.
- 15 Coon WW. Risk factors in pulmonary embolism. *Surg Gynecol Obstet* 1976;143:385-90.
- 16 Morrell MT. The incidence of pulmonary embolism in the elderly. *Geriatrics* 1970;25:138-53.
- 17 Ansari A. Acute and chronic pulmonary thromboembolism: current perspectives. Part II: Etiology, pathology, pathogenesis, and pathophysiology. *Clin Cardiol* 1986;9:449-56.
- 18 Smith GT, Dammin GJ, Dexter L. Postmortem arteriographic studies of the human lung in pulmonary embolization. *JAMA* 1964;188:143-51.
- 19 Tomaszefski JF, Davies P, Boggis C, Greene R, Zapol WM, Reid LM. The pulmonary vascular lesions of the adult respiratory distress syndrome. *Am J Pathol* 1983; 112:112-26.
- 20 Blaisdell FW, Lim RC, Amberg JR, Choy SH, Hall AD, Thomas AN. Pulmonary microembolism. *Arch Surg* 1966; 93:776-86.
- 21 Blaisdell FW, Lim RC, Stallone RJ. The mechanism of pulmonary damage following traumatic shock. *Surg Gynecol Obstet* 1970;130:15-22.
- 22 Schneider RC, Zapol WM, Carvalho AC. Platelet consumption and sequestration in severe acute respiratory failure. *Am Rev Respir Dis* 1980;122:445-51.
- 23 Rodvien R. Hematologic observations made in patients with acute respiratory distress syndrome in the cooperative ECMO project. *Artif Organs* 1978;2:12-8.