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EDITORIAL

Intravascular Coagulation Associated with the Adult Respiratory Distress Syndrome

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In seven of 30 consecutive patients with the adult respiratory distress syndrome, disseminated intravascular coagulation (DIC) developed. Increasing respiratory dysfunction characterized by decreased effective static compliance and increased hypoxemia coincided with the development of DIC. Patients in whom DIC developed were characterized by a high incidence of bleeding, gangrene of the extremities, renal dysfunction, mortality and autopsy evidence of fibrin microthrombi in the lungs, kidney and skin.

In 12 of 23 patients who did not meet the criteria for DIC, the platelet count decreased by at least 50 per cent of the initial values at some time during their illness. Fibrin microthrombi were found in the lungs in the majority of the patients subjected to autopsy. These data support the concept that deposition of platelets on damaged pulmonary capillary endothelium may be more common in the adult respiratory distress syndrome than the DIC syndrome.

The adult respiratory distress syndrome is characterized by diffuse pulmonary capillary endothelial injury [1] leading to predictable clinical, physiologic and pathologic manifestations [2]. A relationship between pulmonary capillary endothelial damage and thrombocyte function has been demonstrated in experimental animal models [3–6]. Such injury in dogs and rabbits has resulted in a prolonged platelet transit time through the lung and decreased platelet recovery from the lung compared to animals with normal pulmonary vasculature. Moreover, decreased platelet recovery was correlated with a decrease in pulmonary compliance and an increase in physiologic shunting. Histologically, platelet thrombi were observed in small blood vessels.

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TABLE I Features of Patients with Disseminated Intravascular Coagulation (DIC)

Etiology of ARDS	Platelets Within 72 hr of ARDS (mm^3)	Hypo-tension*	Abnormal Hemorrhage†	Ischemic Necrosis	Autopsy Evidence of DIC‡
Viral pneumonia	56,000§	+	VS	Right forearm and hand (arterial catheter)	No autopsy
Gastric acid aspiration	19,500	+	VS	None	No autopsy
Gastric acid aspiration	119,000	+	VS, GI, P	Right thumb and index finger (arterial catheter)	Lungs, kidneys, skin
Gastric acid aspiration	38,000§	–	VS, GI	All extremities	Lungs, kidneys, skin
Viral pneumonia	10,000§	–	VS, GI	All extremities	Lungs, kidneys, skin
Pseudomonas aeruginosa septicemia	69,000	+	VS, GI, P	Acrocyanosis	Lungs, kidneys
Noxious gas inhalation	93,000	+	VS	Right thumb and index finger (arterial catheter)	Lungs

NOTE: ARDS = adult respiratory distress syndrome. + = present. – = absent.
* Hypotension was defined by a systolic blood pressure less than 90 mm Hg for 1 hour or longer within 72 hours of beginning PEEP.
† VS = venipuncture sites, GI = gastrointestinal, P = petechiae and/or purpura.
‡ Fibrin microthrombi of small blood vessels was taken as evidence of DIC.
§ Schistocytes seen on microscopic examination of peripheral blood.

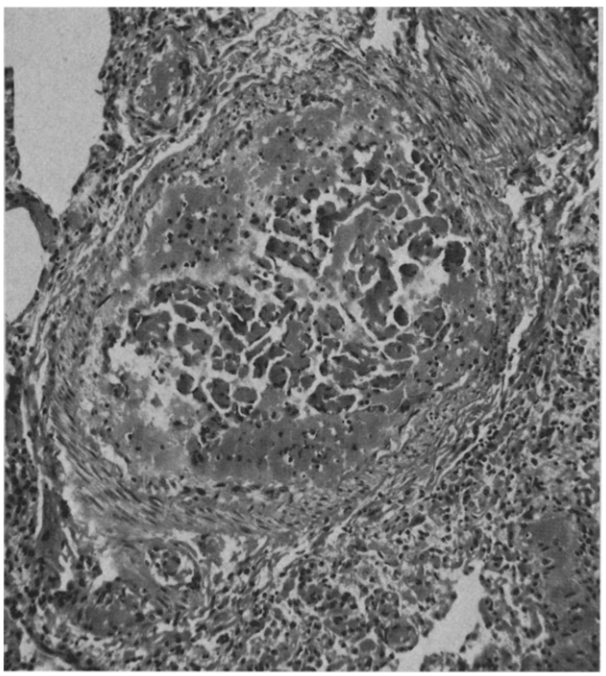

Figure 1. *A small muscular pulmonary artery from one of our patients with DIC. Hematoxylin and eosin stain; original magnification × 100, reduced by 12 per cent. Multiple small vessels were largely occluded by fibrin microthrombi. Beginning fibroblastic proliferation and endothelialization can be seen.*

A possible association between the adult respiratory distress syndrome and the clinical manifestations of intravascular platelet deposition, disseminated intravascular coagulation (DIC), has been suggested by an occasional case report [7,8]. However, a relationship between the adult respiratory distress syndrome and DIC has not been established. This study was undertaken to determine if such exists.

METHODS

The records of 30 consecutive patients with the adult respiratory distress syndrome admitted to the Parkland Memorial Hospital medical intensive care unit from July 1, 1972, to June 1, 1974, were reviewed. All patients were treated by one of us. In order to compare patients with an illness of similar severity, only patients with arterial oxygen tensions (PaO_2) of 70 mm Hg or less, despite inspired oxygen concentrations (F_IO_2) of 50 per cent or greater during assisted ventilation with positive end-expiratory pressure (PEEP), were included. Patients whose adult respiratory distress syndrome was associated with trauma or surgery, or who received blood transfusions or antifibrinolytic agents before the onset of bleeding secondary to intravascular coagulation, were excluded from analysis.

Patients were diagnosed as having DIC only when all the following abnormalities of blood coagulation existed: the platelet count was less than 125,000/mm^3, the Quick prothrombin time was 3 seconds greater than control [9], the activated partial thromboplastin time [10] was greater than

47 seconds, the thrombin time [11] was greater than 25 seconds and fibrin split products, analyzed by the staphylococcal clumping technic [12], were greater than 40 μg/ml.

Two measurements of lung function were analyzed. First, the effective static compliance of the lungs and thorax was determined by dividing the exhaled tidal volume by inflation hold pressure minus the PEEP as measured by the ventilator manometer. Second, the ratio of arterial:alveolar oxygen tension was computed [13]. A value less than 0.75 represents abnormal oxygen transfer by the lung. This ratio was used because it is more reliable than other parameters as an index of gas exchange when comparing patients receiving different concentrations of inspired oxygen [13].

Statistical analysis was performed by Student's t test or Chi square analysis. The probability of an observation occurring by chance alone less than 5 per cent of the time ($P < 0.05$) was considered significant.

RESULTS

In seven of 30 (23 per cent) consecutive patients with adult respiratory distress syndrome, DIC developed. Clinical and pathologic data for these seven patients are recorded in Table I. All patients had clinical as well as laboratory evidence of abnormal blood coagulation. All these patients died. Five of the seven patients who died were examined at autopsy and fibrin microthrombi were present in their lungs (Figure 1); four of five had thrombi in additional tissues (Table I).

Data in patients with DIC are compared with those in patients without intravascular coagulation in Table II. We were unable to distinguish the two groups on the basis of the presumed etiology of the adult respiratory distress syndrome, age, sex, the presence of bacteremia, hypotension, adrenal cortical steroid treatment, renal function, survival or survival time. There was a marked difference in sequential platelet counts in patients in whom DIC developed compared to patients in whom it did not develop (Figure 2).

Respiratory function in the two groups of patients is compared in Figures 3 and 4. In those patients in whom DIC developed oxygen exchange and compliance were significantly worse after the onset of DIC than in those in whom this syndrome did not develop, although the two groups had similarly deranged functions at the outset. In patients with DIC, lung function was also significantly worse after the syndrome developed than it was previously.

In 23 of the patients who did not meet our laboratory criteria for DIC, clinical symptoms of this syndrome did not develop. However, 12 of these patients had a decrease in circulating platelets of at least 50 per cent of their intial values at some time during their illness. Five of these patients who died were subjected to autopsy; two had megakaryocytic hyperplasia of the bone marrow and four had fibrin microthrombi in the lungs but not in other tissues.

TABLE II Comparison of Seven Patients With and 23 Patients Without Disseminated Intravascular Coagulation (DIC)

	Patients With DIC	Patients Without DIC	P
Age (yr, $\bar{M} \pm$ SD)	42 ± 14	38 ± 16	NS*
Men	5	14	NS
Positive blood cultures (%)	57	30	NS
Hypotension (%)†	71	61	NS
Adrenal cortical steroids (%)‡	57	30	NS
Blood urea nitrogen (mg/100 ml, $\bar{M} \pm$ SD)	46 ± 37	19 ± 11	NS
Mortality (%)	100	71	NS
Survival time (days, M ± SD)	8 ± 1	10 ± 3	NS

* NS = not significant ($p > 0.05$).

† Hypotension was defined by a systolic blood pressure less than 90 mm Hg for 1 hour or longer within 72 hours of beginning PEEP.

‡ Each patient received the equivalent of 5 mg/kg body weight of hydrocortisone or more each 24 hours.

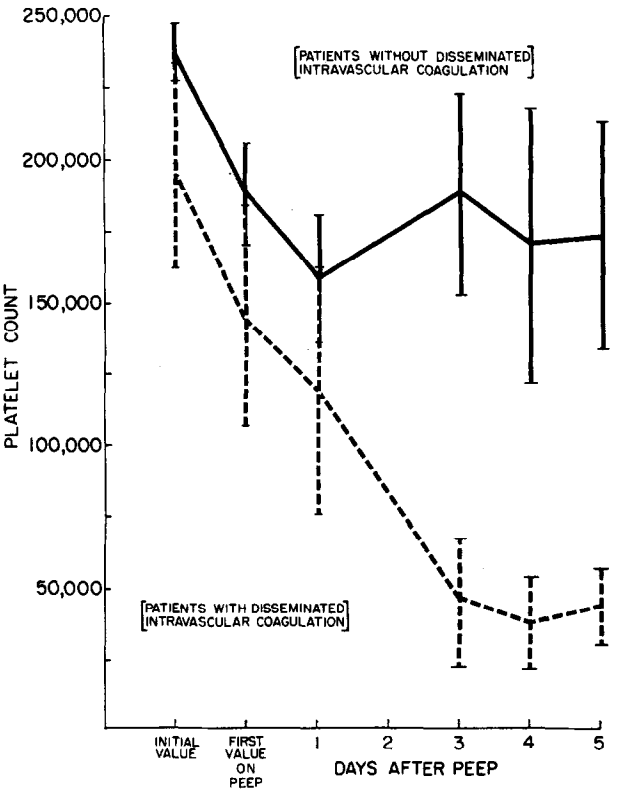

Figure 2. *Platelet count of patients with DIC (continuous line) compared to patients without DIC (dashed line). The brackets indicate 1 standard deviation around the mean value. There are no significant differences between the values initially obtained, when PEEP was begun, or during the first day of PEEP. From the third through the fifth days, the platelet counts are significantly different ($P < 0.05$).*

COMMENTS

Our data indicate that DIC is a frequent complication in patients with severe adult respiratory distress syndrome. The original etiology of the adult respiratory distress syndrome does not apparently alter the likelihood of DIC developing in patients observed in a medical intensive care unit. Our data do not assess the incidence among patients with surgery or blood transfusions; such patients were excluded from this study, since blood transfusions may independently be associated with thrombocytopenia and selective factor deficiencies. Further, only patients with severe hypoxemia necessitating high concentrations of inspired oxygen and the use of PEEP were studied. The role of any of these factors in the genesis or incidence of DIC in the adult respiratory distress syndrome cannot be determined from this report.

Patients in whom DIC developed had the expected clinical manifestations of excessive hemorrhage and ischemic necrosis of extremities. In addition, the onset of DIC was associated with deterioration of pulmonary function indicated by a progressive fall in compliance and worsening of oxygen transfer by the lung. Since these events were coincidental, it is not clear which are cause and which effect.

Many of the patients in whom DIC did not develop had a decrease in circulating platelets during the course of the adult respiratory distress syndrome. At autopsy, four of five of these patients had fibrin microthrombi in the lungs, and two of five had megakaryocytic hyperplasia of the bone marrow. Pulmonary-capillary endothelial-platelet interaction may be the first step in establishing DIC. In our patients without other clinical evidence of DIC, the presence of thrombocytopenia suggests that platelet aggregation may occur frequently in patients with the adult respiratory distress syndrome. Platelet sequestration may be important in altering vascular permeability. Compensatory increase in platelets and coagulation factors may mask the clinical syndrome of DIC in many patients with the adult respiratory distress syndrome. Pathologic evidence of microthrombi in our patients suggest that intravascular coagulation may be a more frequent event in the adult respiratory distress syndrome than the clinical syndrome of DIC.

Our data in conjunction with the experimental models of others [3–6] suggest a causal relationship between

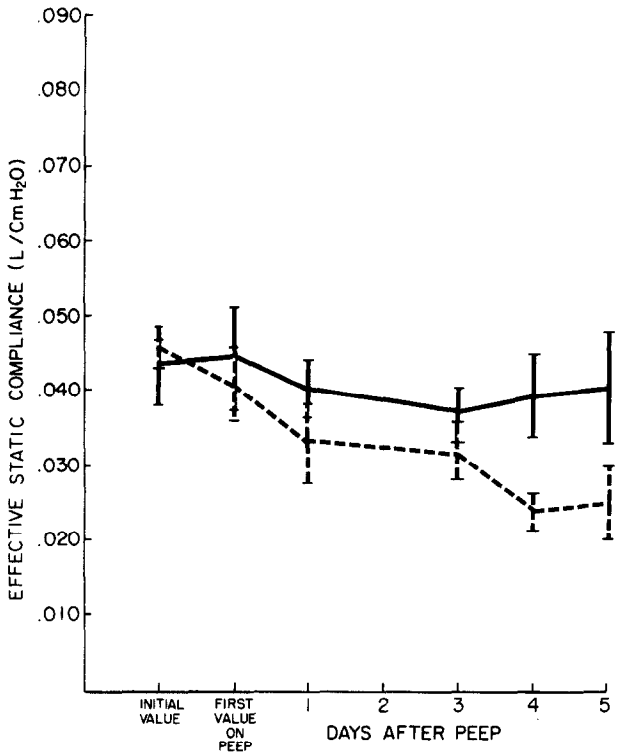

Figure 3. Effective static compliance of patients with DIC (continuous line) compared to patients with DIC (dashed line). The brackets indicate 1 standard deviation around the mean values. Although this measurement of lung stiffness was similar at the onset of disease and of PEEP therapy, those patients in whom DIC developed had significantly lower effective static compliance than patients without DIC ($P < 0.05$).

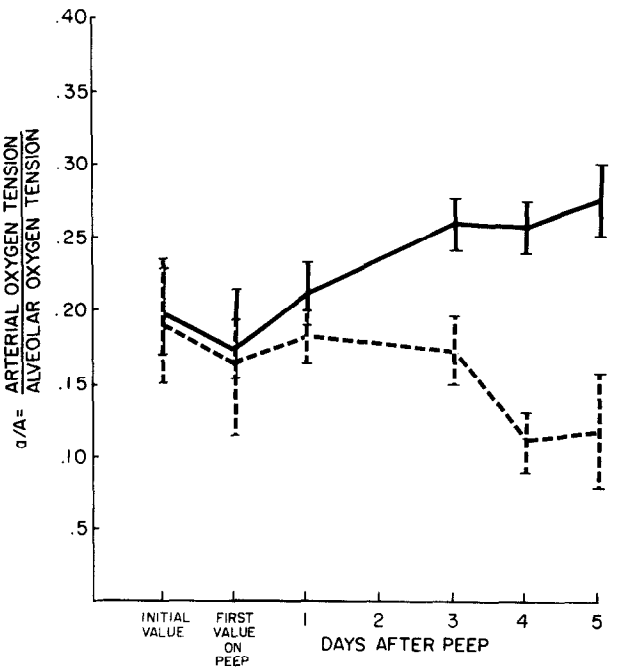

Figure 4. Arterial:alveolar oxygen tension ratio of patients without DIC (continuous line) compared to patients with DIC (dashed line). The brackets represent 1 standard deviation around the mean values. There are no significant differences between the values initially obtained, when PEEP was begun or during the first day of PEEP. From the third through the fifth days, the ratios in two groups are significantly different ($P < 0.05$).

limited intravascular coagulation initiated by damage to pulmonary capillary endothelial cells and a perpetuation of the adult respiratory distress syndrome. The platelet release reaction associated with the adherance of platelets to collagen liberates a variety of vasoactive mediators [14]. It is possible that local changes in pulmonary capillary permeability mediated by these substances compound the existing pulmonary edema. Further clinical and experimental studies are needed utilizing labelled fibrinogen and platelets to delineate the importance of fibrin deposition and intravascular coagulation to acute respiratory insufficiency.

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