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Contact phase of blood coagulation in cardiogenic pulmonary oedema (CPO) and adult respiratory distress syndrome (ARDS)

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Abstract. In order to assess the role of the kallikrein-kinin (k-k) system in the pathogenesis of pulmonary oedema, we studied the contact phase factors of blood coagulation, as well as the haemodynamics and blood gas changes in 34 patients with pulmonary oedema, 23 of them with Adult Respiratory Distress Syndrome (ARDS) and 11 with cardiogenic pulmonary oedema (CPO). We have verified significant differences in the haemodynamic pattern and blood gases between the two groups of patients, which corroborate the previously established differences between both types of pulmonary oedema. Our results reveal k-k system activation in ARDS patients, with a significant fall in factor XII ($p<0.05$), prekallikrein ($p<0.01$), alpha-2-macroglobulin ($p<0.01$) and high molecular – weight kininogens ($p<0.005$), with a rise in C_1-esterase inhibitor ($p<0.001$) in comparison with patients with CPO. All of the CPO patients had normal prekallikrein levels, whereas 15 out 23 ARDS cases (65%) had decreaed prekallikrein values. Our results suggest that the k-k system activation could play a role in the pathogenesis of ARDS. Estimation of prekallikrein levels may be helpful in the differential diagnosis of ARDS.

Key words: Contact system – ARDS – Cardiogenic pulmonary oedema

In 1967, Ashbaugh et al. [1] introduced the concept of Adult Respiratory Distress Syndrome (ARDS) for describing a pattern characterised by dyspnoea, hypoxaemia, reduced pulmonary compliance and oedema in the absence of previous pulmonary disease or heart failure. Since then, many pathogenic theories have been suggested to explain the mechanism of production of the syndrome [2–9]. The pathogenesis of ARDS has not yet been fully established.

The possible role of coagulation and that of primary haemostasis in the development of ARDS has produced contradictory results.

In a previous study [10] we reported k-k system activiation in ARDS patients compared to controls; we also observed a marked positive correlation between the fall in prekallikrein (PPK) levels and the degree of derangement of blood gas and haemodynamic parameters. In that study it was suggested that activation of the k-k system with production of bradykinin, might increase vascular permeability and so bring about or worsen ARDS.

The aim of the present study was to compare the plasma levels of several factors of the k-k system in patients with ARDS and in patients with Cardiogenic Pulmonary Oedema (CPO), in order to establish possible differences which might help in rapidly differentiating both causes, as well as being of use in the diagnosis of pulmonary oedema produced by mixed mechanisms.

Materials and methods

We studied two groups of patients: The first consisted of 23 patients (15 males and 8 females, mean age 45 ± 16 years) with ARDS, whose underlying diseases are summarized in Table 1. In all cases, the diagnosis was made according to criteria previously described by Petty et al. [11]: (1) Clinical history of pulmonary or non pulmonary catastrophic events (but excluding chronic pulmonary disease or left ventricular failure), (2) Clinical respiratory distress (tachypnoea = 20 breaths/min. and laboured breathing), (3) Chest X-ray showing diffuse pulmonary infiltrates (early interstitial, later alveolar), (4) $PaO_2 = 50$ mmHg when Fi O_2 = 0.6 and total respiratory compliance 50 ml/cm H_2O, (5) Increased shunt fraction and dead space ventilation.

Table 1. Age, sex and underlying diseases in patients with ARDS and CPO. A.M.I. = acute myocardial infarction

	ARDS	CPO
Number of patients	23	11
Mean age (mean ± SD)	45 ± 16	50 ± 10
Sex female/male	8/15	2/9
Underlying disease		
Multiple trauma	5	–
Pancreatitis	3	–
Postoperative cardiac surgery	1	–
Bacterial pneumonia	4	–
Peritonitis	4	–
Puerperal sepsis	3	–
Cerebral abscess	2	–
Aspiration pneumonia	1	–
A.M.I.-anterior	–	5
A.M.I.-anteroseptal	–	3
A.M.I.-posteroinferior	–	2
A.M.I.-inferior	–	1

The second group consisted of 11 patients (mean age 50 ± 10 years); all were diagnosed as having CPO after acute myocardial infarction (see Table 1). The diagnosis of myocardial infarction was made on the basis of a compatible clinical history, typical electrocardiographic changes and a 50% increase in Creatininephosphokinase values above normal. Respiratory insufficiency was severe in every patient, all of them requiring O_2 support and mechanical ventilation.

Blood gas and haemodynamic studies were carried out in all patients at the time of diagnosis; within the 24 first hours, simultaneously, blood samples were taken for k-k system parameter determination.

Methods

Blood samples were taken from an antecubital vein and placed in plastic tubes containing 3.8% sodium citrate in a 9:1 proportion. The platelet-poor plasma (PPP) was removed with plastic pipettes after centrifugation of the blood at 2,500 *g*. for 15 min. All samples were immediately stored at −70° until analysis.

The coagulant activity of factor XII was measured by means of a one-stage assay based on the partial thromboplastin time using factor XII deficient plasma as substrate [12]. Plasma prekallikrein was determined by an amidolytic method using S-2302 substrate and prekallikrein activator (AB Kabi Diagnostica, Stockholm, Sweden) as previously described by Gallimore et al. [13]. Plasma functional kallikrein inhibitor assay was performed by the method of Gallimore et al. [13] using purified plasma kallikrein (AB Kabi Diagnostica, Stockholm, Sweden) and S-2302 substrate.

Alpha-2-macroglobulin (α2-M) and high molecular weight kininogen (HMWK) were determined by electro-immunodiffusion [14] using a monospecific antiserum purchased from Behring and Nordic Immunochemical Laboratories respectively. C_1-esterase inhibitor antigen (C_1-Inh) was measured by electroimmunoassay, using an antiserum – against human C_1-Inh (Behringwerke, Marburg, AG, FRG [14]). The results were expressed as percentage of pooled plasma from 20 donors.

Blood gas and haemodynamic parameters

Cardiac output (CO) values were determined by the thermodilution technique using a CO-computer. The mean of three injections was taken.

Systemic pressures were measured via an Argyle catheter placed in the left radial artery.

Pulmonary pressure and pulmonary artery wedge pressure (PWP) were measured through a Swan-Ganz catheter placed in the right pulmonary artery at end expiration and without PEEP. All pressures were recorded with reference to the mid-point of the anteroposterior diameter of the chest, with the patient lying supine. The pressure transducers were connected to the same unit, displaying the pressure curves on a four channel oscilloscope (Hewlett-Packard Mod. 78303).

Samples of mixed arterial and venous blood were taken from the canalized radial artery and Swan-Ganz catheter respectively and blood gases were measured using a ABL-2 analyzer. Haemoglobin values, arterial and venous blood O_2-saturation were calculated with a OSH-2 haemoximeter. Capillary O_2 content and venous O_2 content were obtained according to conventional methods [15]. All the patients were ventilated with $F_iO_2 = 0.6$.

The static thoracic compliance (C_{th}) was measured with the patient in a relaxed state with the tidal volume corrected for the compression volume of the ventilator tubing.

The following formulas were used to calculate the blood gas and haemodynamic values:

$$\text{Cardiac Index (CI)} = \frac{\text{CO}}{\text{Body Surface Area (BSA)}}\ \text{L/mm}^2$$

$$\text{Mean pulmonary artery pressure } (\overline{\text{PAP}}) = \frac{\text{SPAP} + 2\,\text{DPAP}}{3}\ \text{mmHg}$$

$$\text{Pulmonary vascular resistance (PVR)} = \frac{\overline{\text{PAP}} - \text{PWP}}{\text{CO}}\ \text{mmHg/L/min}$$

$$\text{Oxygenation Index } (IO_2) = \frac{P_aO_2}{F_iO_2}$$

$$\text{Right to left shunt } (Qs/Qt) = \frac{C_c - C_a}{C_c - C_v}\ \%$$

$$\text{Static thoracic compliance } (C_{th}) = V_t/\text{Pressure/cm}H_2O$$

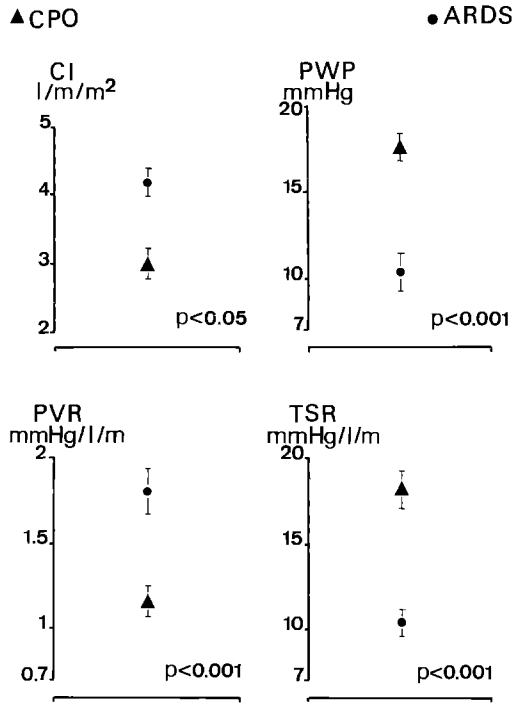

Fig. 1. Mean ± SEM of cardiac index (CI), pulmonary wedge pressure (PWP), pulmonary vascular resistance (PVR) and total sistemic resistance (TSR), in patients with ARDS and CPO

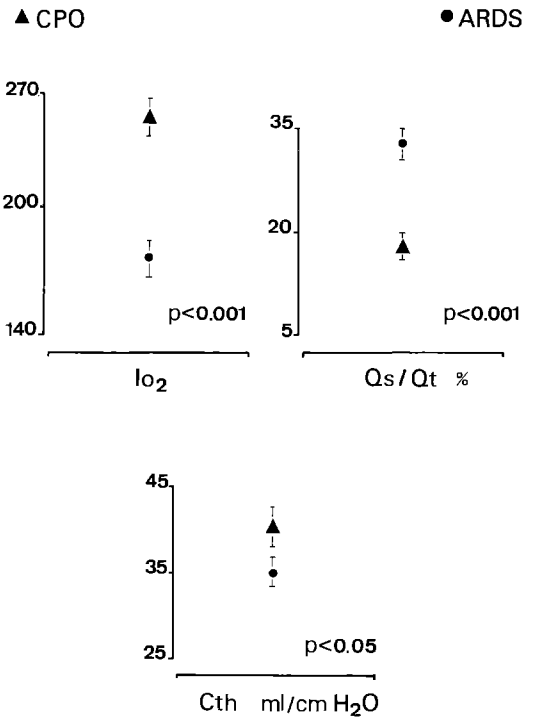

Fig. 2. Mean ± SEM of oxygenation index (IO_2), right to left shunt (Qs/Qt) and static thoracic compliance (Cth) in ARDS and CPO

Statistical methods

Statistical significance was assessed by the unpaired Student's test.

Results

Figure 1 shows the haemodynamic values found in both groups of patients. The haemodynamic pattern of CPO patients showed higher PWP and TSR values in comparison to those of ARDS patients (PWP values of 17.6±1.4 and 11±4.5 respectively, ($p<0.001$); TSR values of 18.1±3.4 and 11±2.5 respectively, ($p<0.001$). In contrast, CI and PVR were significantly lower in CPO than ARDS patients (CI = 3.01±0.4 and 4±0.95 respectively ($p<0.001$). PVR = 1.17 ±0.28 and 2±0.87 respectively ($p<0.001$) (see Fig. 1).

Figure 2 shows the blood gas parameters found in both groups. Patients with ARDS had more severely impaired respiratory function, with IO_2 and C_{th} significantly decreased in relation to CPO patients (174±51 vs. 255±27, $p<0.001$, and 35±6.8 vs. 40±6.9 $p<$, respectively). In contrast, Qs/Qt was significantly hihger in ARDS cases (3.3±9.1 vs. 18.4±1.8, $p<0.001$) (see Fig. 2).

k-k system measurements carried out in both groups are shown in Figures 3 and 4. It was found that ARDS patients had decreased values of factor XII (71±2% vs. 106±7.2, $p<0.05$), PPK (52±4.8% vs. 95.6±5.6, $p<0.001$), a_2-M (55±3.3 vs. 86.7±11.2, $p<0.001$), and HMWK (78.7±3.7 vs. 135±7.5, $p<0.005$) compared to patients with CPO. There was no significant difference between functional kallikrein inhibitory activity (KKI) levels in both groups (104±2.6 and 98.6±4.1, ns). C_1 INH values were significantly higher in ARDS patients when compared to the CPO group (126±3.1 and 102±4.5 respectively, $p<0.001$).

In the present study a ratio of 0.96±0.01 between KKI (by a chromogenic substrate assay) and C_1 INH concentration, was found when samples from CPO cases were examined. This ratio was significantly decreased in ARDS patients (0.70±0.04) in comparison to the CPO group ($p<0.025$).

All of the PPK plasma levels found in CPO patients, were within normal range in our laboratory (109±36 mean ±2 SD of 20 determinations carried out in healthy controls). In contrast, 15 out of 23 ARDS patients (65%) showed PPK levels below normal (mean±SD) (Fig. 5).

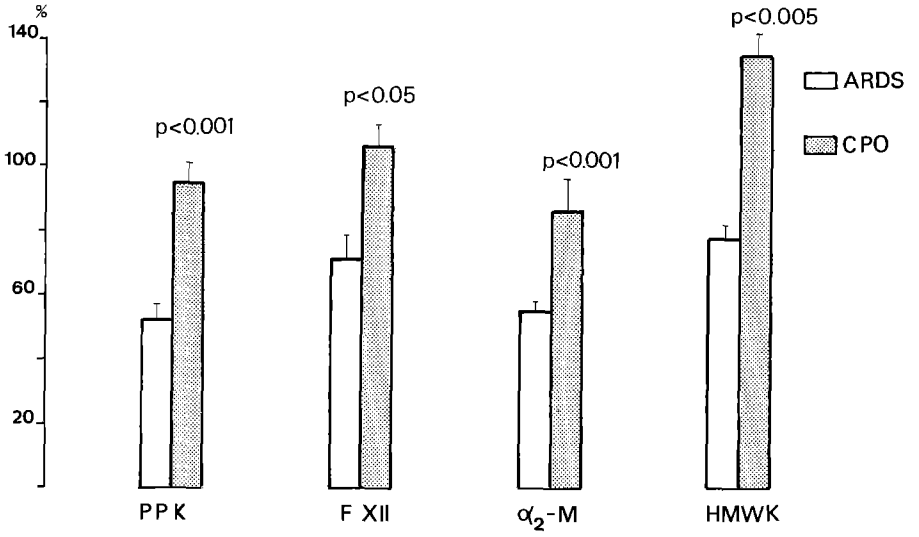

Fig. 3. Mean ± SEM of prekallikrein (PPK), factor XII (F XII), alpha-2-macroglobulin (α-2-M) and high molecular weight kininogen (HMWK), in ARDS and CPO groups

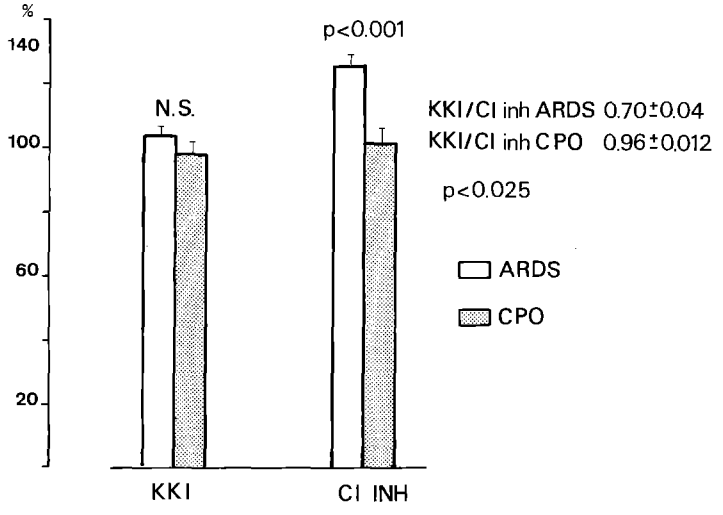

Fig. 4. Mean ± SEM of functional kallikrein inhibitory activity (KKI) and C_1 esterase inhibitor antigenic (C_1 INH) in ARDS and CPO patients. KKI/C_1 INH-ratio between both values

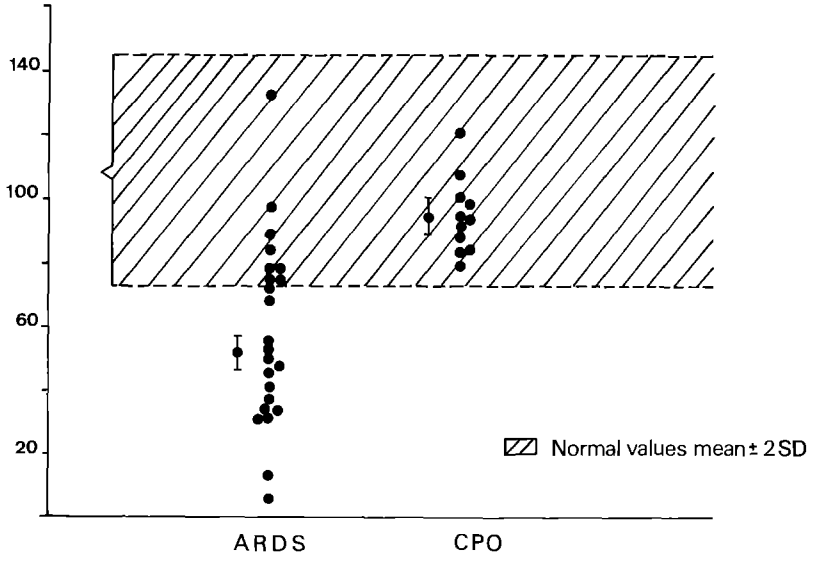

Fig. 5. Values of PPK in ARDS and CPO patients. Shadowed area indicates normal range

Discussion

The results of our study reveal k-k system activation in patients with ARDS compared to those with CPO.

From the haemodynamic point of view, our data confirm earlier works [16, 17] which show distinct haemodynamic and blood gas patterns in ARDS and CPO. Our results agree with those reported by Zapol and Schneider [18] for patients with the same level of cardiac index, and we confirm their observations where pulmonary arterial hypertension and high PVR are characteristic of ARDS. PWP values, in contrast, are within normal with elevated CI and decreased TSR.

Other blood gas data also concurs with the work of Siegel et al. [19], with the finding of more pronounced changes in blood gases in patients with ARDS. There are probably several reasons for – these findings, since the shunt fraction is not exclusively related to the increase in pulmonary extravascular water. Other factors also contribute to its production, such as cardiac output, O_2 pressure and loss of hypoxic vasoconstriction. Through this latter mechanism, the perfusion of units with very low ventilation/perfusion ratios is possible.

Our results show an activation of the k-k system in patients with ARDS (with a decrease in levels of factor XII, PPK, α_2-M and HMWK and a rise in C_1 INH concentration) in contrast to those in CPO group, in which there is no activation. We have found an alteration of the KKI/C_1 INH ratio. This altered ratio is caused by an increase in C_1 INH levels. This discrepancy between the functional and antigenic levels of the inhibitor may reflect the presence of circulating complexes between kallikrein and inhibitor. This hypothesis had recently been confirmed by Nuijens et al. [20]. The authors found increased levels of both factor $XII_a - C_1$ INH and kallikrein/C_1 INH complexes in ARDS patients.

The end result of k-k system activation is the production of the vasoactive peptide bradykinin which may induce pulmonary damage by increasing vascular permeability and causing interstitial oedema. We have already reported this phenomenon in ARDS patients [10], in patients with septic shock [21], the newborn with respiratory distress [22] and in dogs with experimentally induced respiratory distress [23].

Although the haemodynamic and blood gas patterns allow clear differentiation between CPO and ARDS in most cases, clinical situations may exist in which the differential diagnosis is complicated; for example with pulmonary oedema occurring after acute myocardial infarction, aspiration of gastric contents, or in neurogenic pulmonary oedema induced by cerebral anoxia after cardiac arrest. An accurate diagnosis of the type of oedema is of vital importance in the correct treatment of the patient and many methods have been described to demonstrate an increase of pulmonary vascular permeability for liquids and proteins, for example using injected or inhaled radiotracers [24], or measuring the protein content of oedema [25]. All these methods require time and advanced technology. We suggest that the measurement of k-k system parameters may be useful in the differential diagnosis in this group of patients, as contact system activation has not been documented in CPO patients. Further work in this area is necessary in order to determine the usefulness of these measurements.

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