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Research Article

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Endotoxin-induced Pulmonary Dysfunction Is Prevented by C1-Esterase Inhibitor

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Abstract

In septic shock, hypotension, disseminated intravascular coagulation, and neutrophil activation are related to the activation of the blood coagulation contact system. This study evaluates in dogs the effect of the C1-esterase inhibitor (C1-INH), a main inhibitor of the blood coagulation contact system, on the cardiovascular and respiratory dysfunction associated with endotoxic shock. Two groups were included: controls, which received *Escherichia coli* endotoxin, and a C1-INH group in which C1-INH was infused before *E. coli* endotoxin administration.

In both groups, endotoxin produced hypodynamic shock; however, the decrease in the systolic index and the ventricular systolic work indexes were greater in controls than the C1-INH group. In controls, the arterial O₂ partial pressure decreased by 30% and the alveolo-arterial O₂ difference increased by 625%, these parameters remained unchanged in the C1-INH group. Hypoxemia was associated with increased intrapulmonary shunt, decreased blood coagulation contact factors, and decreased C3c. In contrast, C1-INH administration prevented endotoxin-induced hypoxemia, the increase in intrapulmonary shunt, and the decrease in blood coagulation contact factors.

This study shows that, in dogs with endotoxic shock, pulmonary dysfunction is associated with an activation of the blood coagulation contact phase system. An inhibition of this system by C1-INH prevented the hypoxemia induced by endotoxic shock. (*J. Clin. Invest.* 1993. 91:2754-2760.) Key words: acute respiratory distress syndrome • C1-esterase inhibitor • coagulation • endotoxins • hypoxemia

Introduction

Gram-negative bacteremia produces multiorgan dysfunction, septic shock, and frequently death (1-7). The pathogenic factors and mechanisms involved in septic shock are still unclear.

Endotoxin may directly impair the cardiac function. Several authors have observed that the intravenous administration of endotoxin produces a deterioration of cardiac function; this negative effect is independent of cardiac filling pressure and systemic vascular resistance (8-12).

In addition, endotoxin may induce multiorgan dysfunction by an activation of the coagulation pathways at multiple sites.

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Endotoxemia increases plasma protease activity (13-17) and promotes the activation of the blood contact system contributing to disseminated intravascular coagulation, hypotension, and neutrophil activation (18). It appears that endotoxin activates the coagulation through both a direct effect and by influencing endothelial cell function (19-22). Pulmonary dysfunction due to acute respiratory distress syndrome (ARDS)¹ occurs in 25-40% of patients with endotoxemia (23, 24). Microscopic examination of lung tissues from ARDS patients shows damage in both alveolar epithelial cells and capillary endothelium. This is accompanied by a hemorrhagic intra-alveolar exudate high in platelets, fibrin clotting factors, and plasminogen (25, 26). Recently, Idell et al. (27) have documented that both tissue factor VII procoagulant activity and extrinsic pathway inhibitor activity were increased in bronchoalveolar lavage of ARDS patients. In addition, Bertozzi et al. (28) have shown an increase in antifibrinolytic activity in the bronchoalveolar lavage of patients with ARDS. These studies suggest that an alteration in blood coagulation and fibrinolysis may play a role in the pathogenesis of ARDS induced by endotoxemia.

In a previous report, we observed decreased plasma levels of prekallikrein (PK) in patients with ARDS (29); this finding was considered a result of the activation of the contact phase of blood coagulation (29, 30). In these patients, the decrease in plasma PK levels correlated with the degree of pulmonary dysfunction. By contrast, plasma PK levels were unchanged in patients with cardiogenic pulmonary edema which is not associated with structural pulmonary damage (31). Taken together these results suggest that an activation of the blood coagulation contact system could be a factor in the pathogenesis of endotoxin-induced ARDS.

C1-esterase inhibitor (C1-INH) is the main inhibitor of the blood coagulation contact system (32, 33). In that hypotension, disseminated intravascular coagulation and neutrophil activation are consequences of activation of the contact system, its inhibition by administration of C1-INH may help to prevent endotoxin-induced organ dysfunction (22, 34, 35).

1. Abbreviations used in this paper: AP, arterial pressure; ARDS, acute respiratory distress syndrome; A-aDco₂, alveolo-arterial O₂ difference; a-vDco₂, arterio-venous O₂ difference; C1-INH, C1-esterase inhibitor; CI, cardiac index; CO, cardiac output; CVP, central venous pressure; HR, heart rate; LVSWI, left ventricular systolic work index; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; O₂-Deliv, O₂ delivery; PaCO₂, arterial CO₂ partial pressure; PaO₂, arterial O₂ partial pressure; PCWP, pulmonary capillary wedge pressure; PK, prekallikrein; Pvo₂, mixed venous blood O₂ partial pressure; PVRI, pulmonary vascular resistance index; Qs/Qt%, intrapulmonary shunt; RVSWI, right ventricular stroke work index; SATaO₂, arterial O₂ saturation; SATvo₂, mixed venous blood O₂ saturation; SI, systolic index; SVRI, systemic vascular resistance index; VO₂, O₂ consumption.

The aim of this study was to evaluate the effect of inhibition of the blood coagulation contact system on the cardiovascular and respiratory function in an animal model of endotoxic shock.

Methods

Animal model. The study was performed in mongrel dogs (22–32 kg). During the 24-h period before the experiment, the dogs were allowed access to water but not food. 1 h before the initiation of the study, the dogs received droperidol (2.5 mg) and fentanyl (0.05 mg) intramuscularly. Anesthesia was induced by i.v. administration of sodium pentobarbital (15 mg/kg of body weight), pancuronium bromide (0.1 mg/kg of body weight), and fentanyl (0.05 mg/kg of body weight). An endotracheal tube was placed and ventilation was maintained using a volumetric respirator (Pulmelec, Manufacturas Medicas, Madrid, Spain). The ventilatory parameters were: tidal volume 15 ml/kg of body weight; fraction of inspired oxygen (F_{iO_2}) = 0.5 mixed with nitrogenous-protioxide ($N_2 O_2$); pulmonary end-expiratory pressure (PEEP) = 5 cm H_2O ; respiratory rate between 12 and 15 rpm maintaining the partial pressure of arterial carbon dioxide (P_{aCO_2}) at 32–35 mm Hg.

An indwelling catheter was inserted into the femoral artery for blood pressure monitoring and blood sampling. A triple-lumen thermodilution Swan-Ganz catheter (Edwards Laboratories AHS, Añasco, Puerto Rico) was introduced through an upper limb vein and advanced into a main pulmonary artery. Both the Swan-Ganz and the arterial catheters were connected to pressure transducers (model 21080A, Hewlett-Packard Co., Palo Alto, CA) previously leveled with the right atrium. Pressure measurements and electrocardiogram were recorded using a four-channel amplifier (model 7754B, Hewlett Packard Co.).

Cardiac output (CO) was measured by the thermodilution technique (cardiac output computer model 9520, Edwards Laboratories); each value was the mean of three consecutive determinations.

Study protocol. The dogs were divided into two groups: (a) a control group ($n = 8$), in which *Escherichia coli* endotoxin (2 mg/kg) was infused intravenously during a 10-min period, (*E. coli* acetone powder, serotype 026:B6 strain ATCC 12795, Sigma Chemical Co., St Louis, USA); (b) an experimental group ($n = 8$), which received *E. coli* endotoxin as in the control group and an i.v. injection of the contact system inhibitor, C1-INH (500 IU) (Behring Institute, Marburg, FRG). The C1-INH was administered 30 min before the infusion of *E. coli* endotoxin.

The following hemodynamic parameters were measured immediately before and at 60, 120, and 180 min after the administration of the endotoxin: arterial pressure (AP), heart rate (HR), pulmonary arterial pressure (PAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), CO, partial pressure of arterial oxygen P_{aO_2} , P_{aCO_2} , partial pressure of mixed venous blood oxygen (P_{vO_2}), arterial oxygen saturation ($SATaO_2$), mixed venous blood oxygen saturation ($SATvO_2$), and hemoglobin.

The following hemodynamic and pulmonary function parameters were calculated based on previously published formulas (36, 37): mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP), cardiac index (CI), systolic index (SI), left ventricular systolic work index (LVSWI), right ventricular systolic work index (RVSWI), systemic vascular resistance index (SVRI), pulmonary vascular resistance index (PVRI), alveolo-arterial oxygen difference ($A-aD_{CO_2}$), arterio-venous oxygen difference ($a-vD_{CO_2}$), intrapulmonary shunt ($Q_s/Q_t\%$), oxygen consumption (VO_2), and O_2 delivery (O_2 -Deliv). Body surface area (BSA) was calculated using the formula, $BSA = 0.112 \times \sqrt{(\text{weight})^2}$ (38).

Blood samples were obtained at the same time interval for evaluation of blood contact phase, complement systems, and cell count.

Blood gases. P_{aO_2} , P_{aCO_2} , and pH were measured with a blood gas analyzer (Radiometer, BM-S2, Copenhagen, DK).

Hemoglobin levels, $SATaO_2$, and $SATvO_2$ were measured by an oximeter (OSM 2, Hemoximeter, Radiometer). Mixed venous blood samples were collected from the distal portion of the Swan-Ganz catheter.

Sampling procedures and assays. Blood samples were obtained from the proximal lumen of the Swan-Ganz catheter and placed into plastic tubes containing either 3.8% sodium citrate or EDTA. Platelet-poor plasma was obtained from blood samples centrifuged for 15 min at 2,500 g. All samples were stored at $-70^\circ C$ until the day of the assay.

Routine coagulation tests were performed using standard methods (39). The coagulant activity of factors XII and XI was measured by a one-stage assay based on the partial thromboplastin time using as substrate factor XII- and XI-deficient plasma (39). Plasma PK levels were measured by the method of Gallimore et al. (40), using S-2302 as substrate and a PK activator (AB Kabi Diagnostica, Stockholm, Sweden); before activation, platelet-poor plasma was incubated with acetone at $0^\circ C$ for 15 min; the activation with PK activator was maintained for a period of 5 min.

The changes in C1-INH activity and plasma concentration of C1-INH antigen were assessed in two additional dogs of each group. Plasma levels of C1 inhibitor antigen in blood samples were estimated using rocket immunoelectrophoresis (41). Briefly, a 1% (wt/vol) agarose over gel Bond film with 37.5 mM Tris, 100 mM glycine (pH 8.6) for both gel and electrophoresis buffer, and 3% human C1 inhibitor antiserum (Behringwerke, Marburg, FRG). Incubation lasted 12 h at 10 V/cm, then it was cooled with tap water. Human C1 inhibitor was used as reference to estimate the amount of C1 inhibitor in the experimental blood sample. After electrophoresis, the plates were maintained for 3 d in a Petri dish with 0.9% NaCl to eliminate nonreacting proteins. The endotoxin-treated dog plasma was supplemented with human C1 inhibitor to increase the precipitin lines against C1 inhibitor antibodies (42).

The activity of C1-INH was measured by an amidolytic method (kit from Immuno SA Laboratory, Barcelona, Spain) using an excess of C_1 -esterase and $C_2H_5Co-Lys(E-Cbo)-Gly-Arg-pNa$ as substrate.

The fraction C3c of complement was also determined by electroimmunodiffusion (41), using a dog C3c antiserum (Nordic Immunochemical Laboratory, Tilburg, The Netherlands).

Statistical methods. The results are expressed as the mean \pm SE of the absolute values and the percent change from baseline. Comparisons between means were made by ANOVA followed by test of Sheffee for multiple comparison. Statistical significance was defined as a $P < 0.05$.

Results

Systemic and pulmonary hemodynamics. Baseline hemodynamic parameters from both groups are presented in Table I.

The percent changes in MAP, PCWP, MPAP, and CVP are summarized in Fig. 1. In both groups, the MAP decreased progressively throughout the experimental period. The decrement in MAP was similar in both groups. In the control group, the MAP decreased from 125 ± 5 to 81 ± 4 mm Hg at 180 min, and in the C1-INH group from 129 ± 6 to 85 ± 4 mm Hg. The fall in MAP occurred despite no change in cardiac filling pressures (CVP and PCWP). In contrast, in both groups, the MPAP remained unchanged during the study period.

Ventricular function. Changes in HR, CI, SI, LVSWI, RVSWI, SVRI, and PVRI are expressed in Table II and Fig. 2. Basal values were similar in both groups (Table I). The CI and SI decreased in both groups while HR remained unchanged. The decline in CI and SI was associated with a concomitant decrease in LVSWI and RVSWI. The degree of decrease in parameters reflecting ventricular function was not the same in both groups. Whereas in the control group CI, LVSWI, and RVSWI decreased progressively throughout the experiment, in

Table I. Baseline Data in Control and C1-INH Groups

	Hemodynamic parameters									
	MAP	PCWP	MPAP	CVP	HR (b.p.m.)	CI	SI	LVSWI	RVSWI	SVRI
	mm Hg	mm Hg	mm Hg	mm Hg		L/min per m ²	ml/m	g·m	g·m	dyn·s per cm ⁻⁵
Control	125±5	10.8±2.5	16.8±1.4	8.3±2.1	111±9	3.5±1.1	28.3±5.8	48±7.5	4.8±0.9	2788±459
C1-INH	129±6	10.1±1.9	16.1±2.1	8.8±1.7	118±10	3.3±0.9	30.5±7.9	49±8.1	4.2±1.1	2818±503

	Gasometric				
	PaO ₂	A-aDO ₂	Qs/Qt%	Vo ₂	O ₂ Deliv
	mm Hg	mm Hg	%	ml/min	ml/min
Control	295±11	21.3±9	1.8±0.7	169±28	624±130
C1-INH	298±13	23.3±8	1.9±0.6	152±29	631±117

	Blood coagulation			
	Factor XII	Factor XI	PK	C3c
	%			
Control	87±13	92±7	104±22	106±19
C1-INH	89±17	96±9	100±16	92±13

Data are given as means±SE.

the C1-INH group these parameters decreased rapidly during the first 60 min and remained stable until the end of the study period.

The SVRI did not change in either group; the PVRI increased significantly at 120 and 180 min only in the control group.

Alveolo-capillary gas exchange. In the control group the PaO₂ decreased rapidly to 78% of the basal value during the first 60 min of the study period, (from 295±11 to 230±23 mm Hg,

$P < 0.001$). The decline in PaO₂ continued until the end of the experiment (206±9 mm Hg, $P < 0.001$ vs. basal values). As opposed to the control group, no significant change in PaO₂ was observed in dogs receiving C1-INH (Fig. 3). The decrease in PaO₂ observed in the control group was associated with an increase in A-aDO₂ and Qs/Qt%. No change in these parameters was observed in the C1-INH group (Fig. 3).

In the control group, both Vo₂ and O₂ Deliv. decreased significantly at 180 and 120 min, respectively (Table III). This

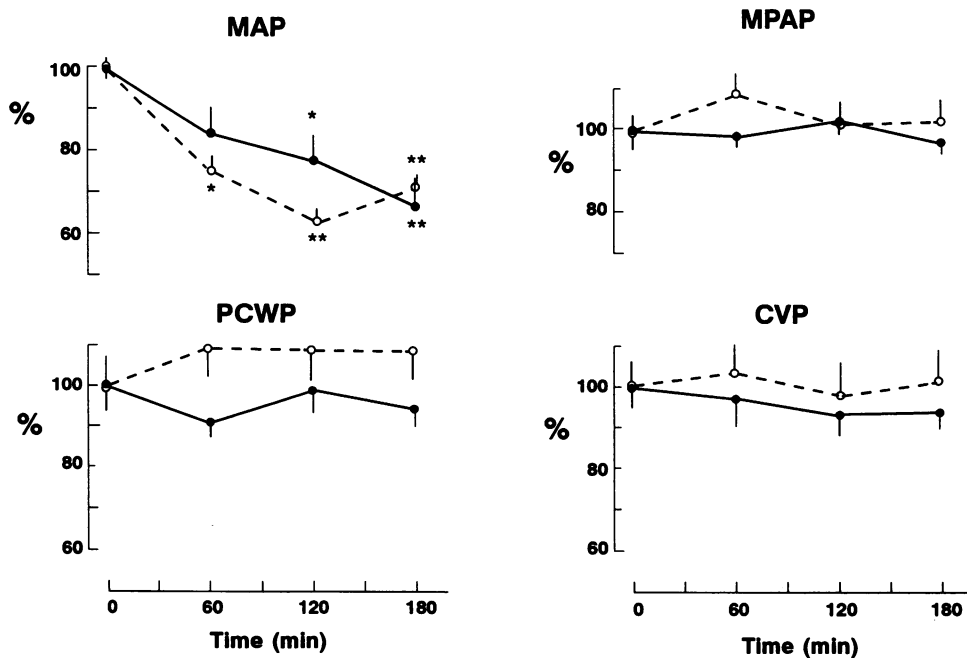


Figure 1. Changes in MAP, MPAP, PCWP, and CVP in two groups of dogs: controls receiving *E. coli* endotoxin (●) and the C1-INH group, which received C1 esterase inhibitor plus *E. coli* endotoxin (○). The results are expressed as the mean±SE percentage of the basal (0 min) value. * $P < 0.05$ vs. basal; ** $P < 0.01$ vs. basal.

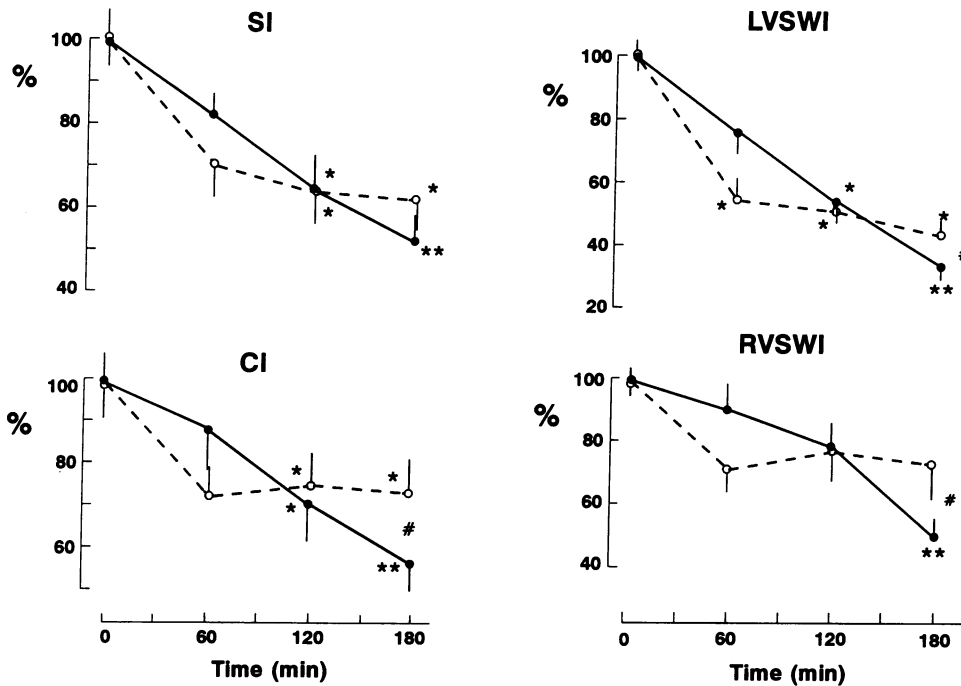


Figure 2. Changes in SI, LVSWI, CI, and RVSWI in two groups of dogs: controls receiving *E. coli* endotoxin (●) and C1-INH group, which received C1 esterase inhibitor plus *E. coli* endotoxin (○). The results are expressed as the mean±SE percentage of the basal (0 min) value. **P* < 0.05 vs. basal; ***P* < 0.01 vs. basal; #*P* < 0.05 vs. control.

decrease coincided with the a marked fall in CI. By contrast, no significant change was observed in VO_2 and O_2 Deliv. in the C1-INH group.

Hematologic parameters. Fig. 4 shows the changes in blood levels of factors XII and XI, PK, and C3c during the study period. The infusion of *E. coli* to the control dogs produced a decrease in blood levels of factors XII and XI. Similar results were observed in the C1-INH group despite the inhibition of the contact system.

In control dogs, the blood levels of PK decreased progressively throughout the study period. The administration of C1-INH prevented the fall in PK. A decrease in C3c levels was observed in both groups. However, at 180 min, the decrease in C3c was more pronounced in control dogs than in those receiving C1-INH. During the 3 h of the experiment, polymorphonuclear cell count decreased in both groups from $5.5 \pm 0.4 \times 10^9$ /liter to $2.8 \pm 0.1 \times 10^9$ /liter (*P* < 0.01) in the controls and from $6.8 \pm 0.4 \times 10^9$ /liter to $2.3 \pm 0.1 \times 10^9$ /liter (*P* < 0.01) in the

Table II. Percent Change in HR, SVRI, and PVRI in Control and C1-INH Groups during the Experimental Period

		Period		
		60	120	180
		min		
HR	Control	106±03	109±05	110±03
	C1-INH	121±07	120±08	121±08
SVRI	Control	98±08	111±07	125±07
	C1-INH	109±08	92±07	105±09
PVRI	Control	141±19	205±21*	220±18*
	C1-INH	143±14	157±10	156±15†

* *P* < 0.05 vs. baseline, † *P* < 0.05 vs. control.

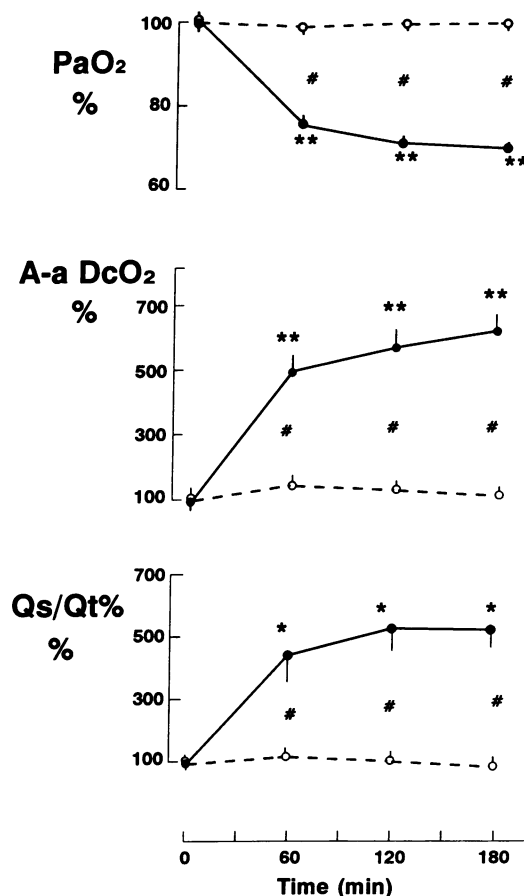


Figure 3. Changes in PaO_2 , A-a DcO_2 , and $\text{Qs}/\text{Qt}\%$ in two groups of dogs: controls receiving *E. coli* Endotoxin (●) and C1-INH group, which received C1 esterase inhibitor plus *E. coli* endotoxin (○). The results are expressed as the mean±SE percentage of the basal (0 min) value. **P* < 0.05 vs. basal; ***P* < 0.01 vs. basal; #*P* < 0.05 vs. control.

Table III. Mean Percent Change in VO_2 , O_2 -Deliv, and $a\text{-vDco}_2$ in Control and C1-INH Groups during the Experimental Period

		Period		
		60	120	180
		min		
VO_2	Control	99±7	82±7	77±7*
	C1-INH	97±9	104±8	108±9‡
O_2 -Deliv	Control	87±9	69±7*	56±14*
	C1-INH	72±8	75±8	75±6‡
$a\text{-vDco}_2$	Control	99±7	82±7	77±8*
	C1-INH	97±10	104±12	108±12

* $P < 0.05$ vs. baseline, ‡ $P < 0.05$ vs. control.

C1-INH group. Mean baseline platelets count was $252 \pm 16 \times 10^3/\text{mm}^3$ and $272 \pm 12 \times 10^3/\text{mm}^3$ in control and C1-INH groups, respectively. Administration of endotoxin with or without C1-INH did not produce significant changes in platelet count.

Changes in C1-INH activity and plasma levels of C1-INH antigen are presented in Fig. 5. In two control dogs, endotoxin administration produced a moderate decrease in both C1-INH activity and plasma levels of C1-INH antigen. In two separate dogs, the administration of C1-INH increased the C1-INH activity and the plasma levels of C1-INH antigen.

Discussion

This study shows that an inhibition of the contact system by administration of C1-INH prevents the hypoxemia associated with experimentally induced endotoxic shock.

In dogs, the administration of *E. coli* endotoxin with or without C1-INH produced hypodynamic shock. The hypoten-

sion was associated with a decrease in CI and SI. This was explained by a decline in LVSWI and RVSWI, which occurred despite no change in cardiac filling pressures. The production of hypodynamic shock suggests a deterioration in cardiac function induced by endotoxin which has been previously described in both animal models and humans (8–12). In both control and C1-INH groups, this hypodynamic state was associated with an increase in $a\text{-vDco}_2$ and a decrease in serum bicarbonate (data not shown).

Whereas in control animals the PaO_2 decreased, this parameter remained unchanged in dogs receiving C1-INH. Thus, the inhibition of the contact system prevents to some extent the alteration in pulmonary function induced by *E. coli* endotoxin. The decrease in PaO_2 produced by *E. coli* endotoxin administration is likely due to the increase in $A\text{-aDco}_2$ and $Q_s/Q_t\%$ and the decrease in VO_2 and O_2 -Deliv. These results suggest that, in our model, endotoxin administration produced the ventilation/perfusion mismatch described in early phases of ARDS (24). The inhibition of the contact system by administration of C1-INH (Fig. 5) prevented the increase in $A\text{-aDco}_2$ and $Q_s/Q_t\%$, and the decrease in VO_2 and O_2 -Deliv. These data suggest that the ventilation/perfusion mismatch seen in ARDS is in part due to an activation of contact system. A possible interpretation for the hypoxemia observed in our model is a change in airway function induced by endotoxemia. Owing to the anatomical characteristics of the trachea and the bronchial tree in the dog, differences between dynamic and static thoracopulmonary compliance are difficult to measure; thus, small differences in airway pressure (< 2 cm H_2O) due to endotoxin may have not been detected. Nevertheless, the differences observed in PaO_2 between the control and C1-INH groups are more likely attributable to an effect on the alveolocapillary exchange than to a change in airway function.

In our control dogs the alteration in pulmonary function was associated with an activation of the contact system as evidenced by a decrease in PK, factor XII, C1-INH, factor XI, and C3c (Figs. 4 and 5). This decrease could not be attributed to

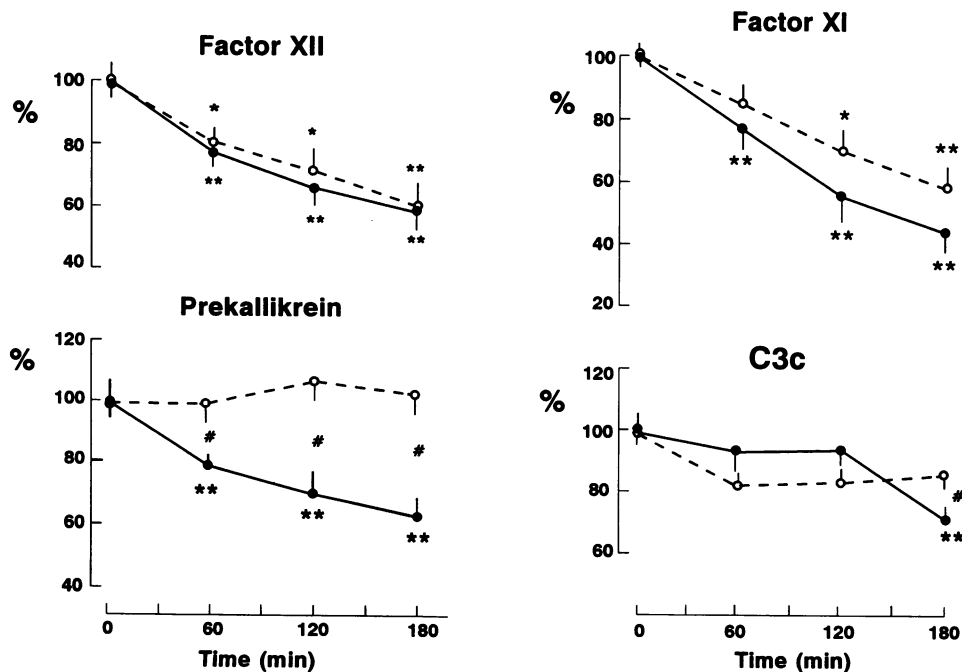


Figure 4. Changes in factors XII and XI, prekallikrein, and fraction C3c of complement in two groups of dogs: controls receiving *E. coli* endotoxin (●) and C1-INH group, which received C1 esterase inhibitor plus *E. coli* endotoxin (○). The results are expressed as the mean±SE percentage of the basal (0 min) value. * $P < 0.05$ vs. basal; ** $P < 0.01$ vs. basal; # $P < 0.05$ vs. control.

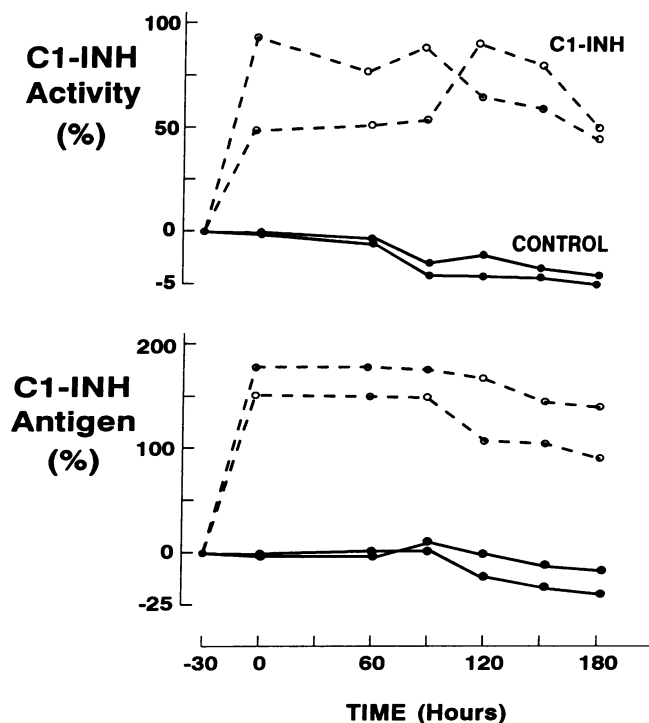


Figure 5. Changes in activity of C1 esterase inhibitor (C1-INH Activity) and in plasma antigen levels (C1-INH Antigen) in two control dogs receiving *E. coli* endotoxin (●) and in two dogs which received C1 esterase inhibitor plus *E. coli* endotoxin (C1-INH group) (○). Results are expressed as percent change from basal values obtained before the administration of endotoxin and C1-INH.

hemodilution in that the hematocrit increased moderately during the experiment and the increase was similar in both groups (data not shown). Previous studies by us and others have shown that, in ARDS patients, the plasma levels of HK, factor XII, and PK were decreased suggesting an activation of the kallikrein-kinin system (29, 30). In our study (29), the decrease in PK levels correlated with the severity of the pulmonary dysfunction; conversely, in patients with pulmonary dysfunction due to cardiogenic pulmonary edema without ARDS, the plasma levels of PK, factor XII, and high molecular weight kininogen were not decreased. Thus, it appears that in ARDS the activation of the contact system is not a direct consequence of the pulmonary edema (31).

Carlson et al. (43) and McGuire et al. (44) have estimated that the activation of the kallikrein-kinin system is the most important factor leading to ARDS. The study of Colman (45) suggested that during the activation of the blood coagulation system, Hageman factor undergoes contact activation with PK in the presence of a cofactor, high molecular weight kininogen, and a negatively charged surface. This originates in the formation of a serine protease, kallikrein. Subsequently, the high molecular weight kininogen releases bradykinin, the final product of the kallikrein-kinin system activation (46). This vasoactive peptide would induce pulmonary damage resulting in an increase in vascular permeability and interstitial edema (44). An activation of PK would also cause the release of elastase by neutrophils (47). Elastase then can produce tissue damage favoring ARDS. In the present study, the administration of endotoxin produced a significant decrease in number of neutro-

phils, however a direct measurement of cell activation is not available.

In addition, endotoxin administration produces an activation of the complement system (48, 49); in our dogs, this activation was suggested by the decrease in C3c. Complement activation leads to deposition of terminal complement proteins C5b-9 on platelets and endothelial cells, with subsequent cellular activation and expression of GMP-140 (50, 51). Subsequently, the activation of GMP-140 induces adhesion and activation of neutrophils creating a vicious circle of activation-induced activation (52). The administration of C1-INH may halt this vicious circle by preventing the activation of complement. This has been suggested by previous studies in rabbits (34) and pigs (35).

The PVRI increased significantly in the control group. This has been attributed to multiple hemodynamic changes including the release of vasoactive peptides during endotoxic shock (53). In dogs pretreated with C1-INH, the PVRI did not increase significantly; this may have been the result of the inhibition of the contact system which could have partially prevented endothelial damage. The observed decrease in RVSWI in the control group may be explained by a negative inotropic effect of endotoxin (11, 12); in dogs receiving C1-INH the decrement in RVSWI was not as marked as in controls, a better oxygenation may have ameliorated the negative inotropic effect of endotoxin.

Finally, the worse hemodynamic conditions observed in the control group may be responsible for the decrease in VO_2 and in O_2 -Deliv, resulting in less O_2 supply to the tissues.

In summary, the administration of *E. coli* endotoxin induces hypodynamic shock and a decrease in PaO_2 . This is associated with an increase in PVRI and an activation of the contact system. The inhibition of the contact system by administration of C1-INH in addition to *E. coli* endotoxin, prevented the decrease in PaO_2 and the increase in PVRI. In conclusion, it is likely that hypoxemia induced by endotoxic shock is mediated by an activation of the contact system.

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