Prostacyclin Reversal of Lethal Endotoxemia in Dogs

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A B S T R A C T   Severe endotoxemia, a condition where microembolization and intravascular coagulation are thought to play important roles, was treated experimentally with prostacyclin (PGI_2). In a study of 24 dogs, 8 control animals injected with 1.75 mg·kg⁻¹ of endotoxin died within 24 h. Six animals given intravenous aspirin 100 mg/kg, 30 min after endotoxin died. 9 of 10 dogs infused with 100 ng $PGI_2 \cdot kg^{-1} \cdot min^{-1}$ for 3 h, given 30 min after the injection of endotoxin survived 24 h ($P < 0.025$). Injection of endotoxin resulted in a: (a) maximal 62% fall in mean arterial pressure ($P < 0.001$); (b) transient doubling of mean pulmonary arterial pressure ($P < 0.001$); (c) initial 70% drop in cardiac index ($P < 0.001$); (d) decline in blood platelets from 213,700 to 13,700/mm³ ($P < 0.001$), and leukocytes from 7,719 to < 750/mm³ ($P < 0.001$); (e) depressed urine output ($P < 0.001$); (f) 34% decrease in blood fibrinogen ($P < 0.01$) and an increase in fibrin degradation products > 50 μg/ml ($P < 0.001$); (g) fivefold increase in circulating cathepsin D titer ($P < 0.005$) and (h) increase in blood norepinephrine ($P < 0.005$), dopamine ($P < 0.005$), and epinephrine ($P < 0.001$). Aspirin treatment led to an increase in mean arterial pressure ($P < 0.001$) and mean pulmonary arterial pressure ($P < 0.005$), but cardiac index, urine flow, platelets, leukocytes, fibrin degradation products, and cathepsin D levels remained similar to untreated controls. After infusion of PGI_2 there was a: (a) prompt increase of cardiac index to base-line levels; (b) late increase in mean arterial pressure ($P < 0.005$) after the discontinuation of PGI_2 treatment (c) restoration of urine output; (d) increase in circulating platelets to

levels still below base line but above untreated control animals ($P < 0.05$); (e) no effect on circulating leukocyte levels; (f) fall in fibrin degradation products to 11.2 μg/ml ($P < 0.05$); (g) decline in cathepsin D levels to values 60% lower than the untreated controls ($P < 0.025$); and (h) reduction in plasma norepinephrine levels to base line at 4 h ($P < 0.005$). Although the mode of PGI_2 action is not clear, it is effective in the treatment of experimental endotoxemia.

INTRODUCTION

Endotoxemia is associated with thrombocytopenia, leukopenia (1–3) and the appearance of platelet and leukocyte aggregates in the microvasculature, particularly of the lungs (4–6). These hematologic events are thought to underlie the hemodynamic alterations of endotoxemia that is pulmonary hypertension, low cardiac output, and systemic hypotension. The precise mechanisms of injury are unknown, but probably include both mechanical vascular obstruction with release of vasoactive and vasotoxic agents directly from the intravascular aggregates, as well as indirect effects mediated by injured organs such as the liver (7). The salutary results of the treatment of pulmonary embolism with an infusion of the antiaggregating and smooth muscle relaxing agent prostacyclin (8) prompted a trial of this prostaglandin in the therapy of endotoxemia; an event thought to be characterized by microemboli and disseminated intravascular coagulation.

METHODS

24 adult mongrel dogs weighing 21–40 kg were anesthetized with sodium pentobarbital 30 mg/kg, paralyzed with pancuronium bromide 0.1 mg/kg (Organon Inc., West Orange, N. J.), and intubated and ventilated with room air using a piston pump (Harvard Apparatus Co., S. Natick, Mass.). Tidal volume was set at 15 ml/kg and the rate at 12

cycles/min. Adjustments in rate were made to yield a $PaCO_2$ of 35–40 mm Hg. Supplemental doses of pentobarbital and pancuronium were added as required to maintain anesthesia and paralysis. A femoral arterial catheter was placed for blood sampling and the measure of mean arterial pressure (MAP)[1] using a strain gauge transducer (model 800, Bentley Laboratories, Irvine, Calif.). The femoral vein was cannulated for fluid and drug administration. A 7 French, thermister-tipped flow directed pulmonary arterial catheter (Instrumentation Laboratory, Lexington, Mass.) was introduced into the external jugular vein and advanced into the pulmonary artery. This catheter was used to measure central venous (CVP), mean pulmonary arterial (MPAP) and pulmonary arterial wedge pressures (PAWP) using strain gauge transducers (Bentley Laboratories). The catheter was also used for pulmonary arterial blood sampling and cardiac output determinations by thermodilution (Instrumentation Laboratory, model 601). Arterial and mixed venous blood gases, pH, hemoglobin and oxyhemoglobin measurements were made with standard Clark and Severinghaus electrodes and by spectrophotometry (Instrumentation Laboratory, models 282 and 813). Transurethral cannulation of the urinary bladder was performed for meaurement of urinary output. Pulmonary vascular resistance (PVR) was calculated from the ratio MPAP-PAWP/CI and systemic vascular resistance (SVR) from the ratio MAP-CVP/CI where CI is cardiac index expressed in ml/min·kg. Leukocyte and platelet counts were performed using EDTA anticoagulated blood and phase microscopy. Fibrinogen was estimated spectrophotometrically after conversion to fibrin according to the method of Swain and Feders (9). Fibrin degradation products (FDP) were measured by staphylococcal clumping according to the technique described by Leavelle et al. (10).

Catecholamine assay. Plasma content of norepinephrine, epinephrine, and dopamine was assayed by a radioenzymatic, thin layer chromatographic procedure (11). Arterial blood samples were collected in heparin and centrifugated at 5,000 g for 10 min at 4°C. Proteins in a 200-μl aliquot of plasma were precipitated by the addition of 200 μl 0.5 M perchloric acid containing 31.8 mM EGTA. The supernatant fluid was separated and an aliquot of 200 μl was incubated for 90 min with catechol-O-methyl transferase and tritiated S-adenosylmethione (New England Nuclear Corp., Boston, Mass.). The reaction was stopped by the addition of borate buffer (pH 8.0) containing metanephrine, normetanephrine (Sigma Chemical Co., St. Louis, Mo.), and 3-methoxy,4-hydroxyphenyl-ethylamine (Calbiochem-Behring Corp., American Hoechst Corp., San Diego, Calif.). The amines were extracted into toluene:isoamyl alcohol (3:2) and then into 0.1 M acetic acid. The radioactive products were separated by thin layer chromatography and the appropriate areas separately scraped into counting vials. After periodate oxidation of the methylated compounds of metanephrine and normetanephrine to vanillin, phosphor-containing toluene was added and the tritium content assayed by liquid scintillation spectrometry.

Cathepsin D. was assayed by a modification of the procedure of Anson (12) and Utsunomiya et al. (13). The substrate was 2.5% denatured bovine hemoglobin (Sigma Chem-

ical Co.) dissolved in 0.28 M acetic acid containing 0.02 M ammonium sulfate (pH 3.7). A volume of 0.25 ml plasma as added to 0.75 ml of this substrate and incubated at 37°C for 3 h. The reaction was stopped by adding 3 ml of 10% TCA. The concentration of the unprecipitated proteolytic product was measured according to the procedure of Lowry et al. (14). Results are expressed as micromoles of tyrosine liberated per milliliter of plasma per hour.

Endotoxin, prepared from *E. coli* (Difco Laboratories, Detroit, Mich.) was dissolved in normal saline (10 mg/ml) just before each experiment. Prostacyclin (PGI_2) supplied by Dr. Pike, Upjohn Co., Kalamazoo, Mich., was also freshly prepared. It was dissolved in 20 mM Tris buffer (pH 10) and infused using a specially designed ice-water jacketed syringe system which maintained infusate temperature <3°C. The rate of drug infusion was 100 ng/kg·min using a volume of 3.3 ml/h. Aspirin (Sigma Chemical Co.) was dissolved in 8.4% sodium bicarbonate in a concentration of 100 mg/ml (pH 9.0).

All dogs received a rapid intravenous injection of 1.75 mg/kg endotoxin. Eight animals were then given the Tris buffer without PGI_2 and served as untreated controls. 30 min after endotoxin administration, an infusion of PGI_2 was started in 10 dogs and was continued over a 3-h period. In six dogs 100 mg/kg aspirin was rapidly injected intravenously 30 min after endotoxin. Hemodynamic measurements, urine output, arterial and mixed venous blood samples were obtained before endotoxin infusion, after 6 min and then at 30-min intervals for 5 h. Hemoglobin levels were kept constant using intravenous infusions of lactated Ringer's solution. Sodium bicarbonate (1 meq/ml) was added to maintain blood pH between 7.35 to 7.40. Heat lamps were used to stabilize body temperature. After 5 h of monitoring, anesthesia was discontinued, pancuronium was reversed with neostigmine 0.06 mg/kg (Roche Diagnostics Div., Nutley, N. J.), and atropine 0.02 mg/kg (Burroughs-Wellcome Co., Research Triangle Park, N. C.). The animals were extubated, observed in their cages for 24 h, and then killed.

Statistical analysis of differences between the three groups was based upon a one-way analysis of variance. Epinephrine values between control and PGI_2 groups were analyzed by a repeated measures analysis of variance. A paired t test was used to examine changes within a group. The Chi-square test was employed for mortality studies (15). All data are expressed as the mean ±1 SE. Figures contain one, two, three or four asterisks (*), indicating a P value of less than 0.05, 0.01, 0.005 or 0.001 between PGI_2 and control groups. Crosses (†) in the figures refer to comparisons between aspirin and control animals.

RESULTS

Hemodynamics. Immediately after endotoxin infusion, MAP fell from 131±3 to 50±5 mm Hg, while MPAP rose twofold (Fig. 1). The CVP and PAWP were unchanged from initial values of 4.7±0.7 and 6.9±0.9 mm Hg, respectively. The CI fell 70% (Fig. 2). These abnormalities were transient and after 30 min there was a partial restoration toward base line.

Infusion of PGI_2 led to a prompt increase of CI to base-line level which was significantly higher than untreated controls. Flow remained high even after cessation of the PGI_2 infusion (Fig. 2). In the aspirin group CI remained low. MAP did not change during PGI_2 but increased from 82 to 97 mm Hg after discontinuation of the drug, and was then higher
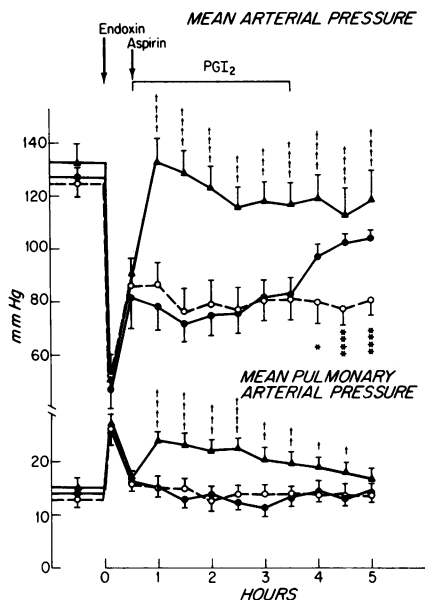
FIGURE 1 MAP fell and MPAP rose following intravenous administration of endotoxin. An increase in MAP in the treated animals became manifest only after discontinuation of the dilating agent PGI_2. MPAP was not affected by PGI_2 therapy. Aspirin administration led to a prompt increase in MAP and MPAP. O, control; ●, PGI_2; ▲, aspirin. † refer to comparisons between aspirin & control animals. *, comparisons between PGI_2 and control animals.

than controls ($P < 0.05$). Aspirin led to a prompt rise in MAP ($P < 0.001$) and MPAP ($P < 0.005$) (Fig. 1). The prompt rise in PVR after endotoxin spontaneously returned toward base line, while PGI_2 further reduced PVR below control values (Fig. 3). In contrast, aspirin led to a significant rise in PVR. SVR did not
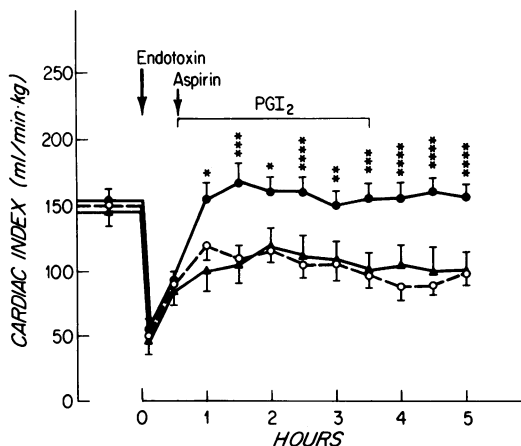

FIGURE 2 CI fell after intravenous infusion of endotoxin and remained low with aspirin. PGI_2 was followed by an early increase in flow which continued after termination of the infusion. O, control; ●, PGI_2; ▲, aspirin. *, comparisons between PGI_2 and control animals.
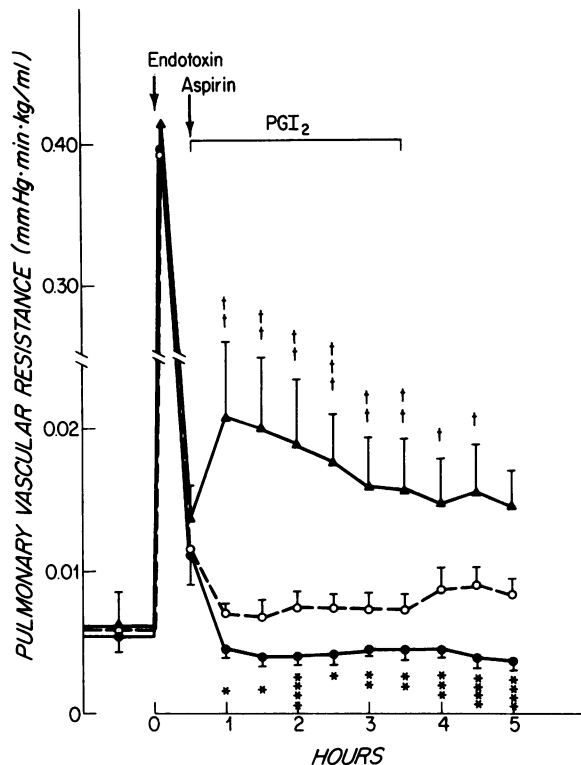

FIGURE 3 PVR rapidly increased following endotoxin. Aspirin led to an increase and PGI_2 infusion was followed by a decrease in PVR below control levels. O, control; ●, PGI_2; ▲, aspirin; †, comparisons between aspirin & control animals; *, comparisons between PGI_2 and control animals.

change following endotoxin. Administration of PGI_2 led to a fall in SVR from 0.89 ± 0.08 mm Hg·min·kg/ ml 30 min following endotoxin to 0.47 ± 0.05 mm Hg·min·kg/ml 30 min following PGI_2 ($P < 0.005$). Aspirin, on the other hand, led to a rise in SVR from 0.98 ± 0.09 mm Hg·min·kg/ml to 1.37 ± 0.16 mm Hg· min·kg/ml ($P < 0.01$) at these same time intervals. There were no changes noted in the CVP or PAWP in either control or treated animals.

Following endotoxin, urine flow fell ($P < 0.01$, Fig. 4). Toward the end of the PGI_2 infusion and after cessation of the drug, urine volumes were restored. Eventually they significantly exceeded ($P < 0.005$) values in the severely oliguric dogs of the control and aspirin group.

Pulmonary function. Physiologic shunting ($\dot{Q}_S/\dot{Q}_T$) increased from 18 ± 1 to $31\pm4\%$ 60 min after endotoxin ($P < 0.005$). The physiologic dead space (V_D/V_T) had risen from 54 ± 3 to $62\pm2\%$ ($P < 0.001$) 6 min following endotoxin. Infusion of PGI_2 did not prevent or reverse the rise in $\dot{Q}_S/\dot{Q}_T$ or cause V_D/V_T to vary from untreated control animals. Aspirin was also ineffective in reversing $\dot{Q}_S/\dot{Q}_T$, but V_D/V_T decreased from $64\pm2\%$ 30
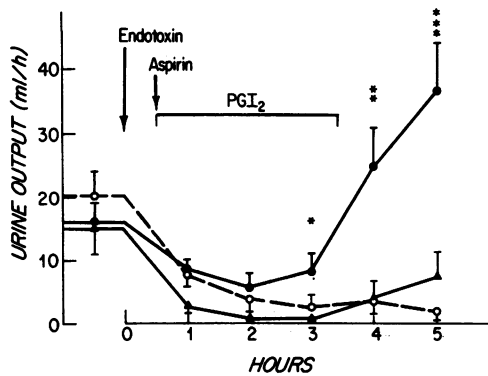
FIGURE 4 Urine output fell after intravenous endotoxin and was unaffected by aspirin. An increase in urine flow was noted toward the end of the PGI₂ infusion. This increase became more prominent after cessation of PGI₂ administration. O, control; ●, PGI₂; ▲, aspirin; *, comparisons between PGI₂ and control animals.

min after endotoxin to 39±3% ($P < 0.001$) at 5 h. In control animals V_D/V_T was 56±3% at this time ($P < 0.005$).

Platelet and leukocyte count. 6 min after endotoxin, platelet numbers decreased to less than 10% of base line ($P < 0.001$) and then gradually increased, reaching a plateau of about 100,000 after 60 min in the control group (Fig. 5). Aspirin did not alter numbers, but with PGI₂ platelets slowly rose and after 2.5 h the count of 122,700±10,300 was higher than controls ($P < 0.05$). The leukocyte count following endotoxin initially declined to <750/mm³ ($P < 0.001$) and then gradually rose to levels above 4,000/mm³ by 5 h. PGI₂ and aspirin were without effect on the leukocyte count.

Fibrinogen and FDP. Fibrinogen levels decreased from 484±52 to 321±28 μg/dl in the control group ($P < 0.01$), from 483±39 to 331±24 mg/dl in the PGI₂ group ($P < 0.005$) and from 464±64 to 227±47 μg/dl in the aspirin group ($P < 0.001$). Fibrinogen remained depressed in the three groups throughout the experiment. 30 min after endotoxin, FDP rose from <0.05 to 36.0±9.6 μg/ml and to 52.0±18 μg/ml at 3 h. In the PGI₂ treated group, FDP peaked at 54.4±20.0 μg/ml and declined significantly ($P < 0.05$, Fig. 6). In the aspirin treated group, FDP increased to 53.7±20.0 μg/ml after 2 h, similar to the control group.

Cathepsin D. Endotoxin injection resulted in a five-fold rise in plasma cathepsin D from 128±79 to 812±145 μM trypsin/ml·h at 3.5 h in the control group ($P < 0.001$, Fig. 7). In the PGI₂ group, cathepsin D levels peaked at 602±162 after 2 h ($P < 0.05$) and became significantly lower than untreated controls by 3.5 h ($P < 0.05$). Cathepsin D levels in the aspirin group were not significantly different from controls.

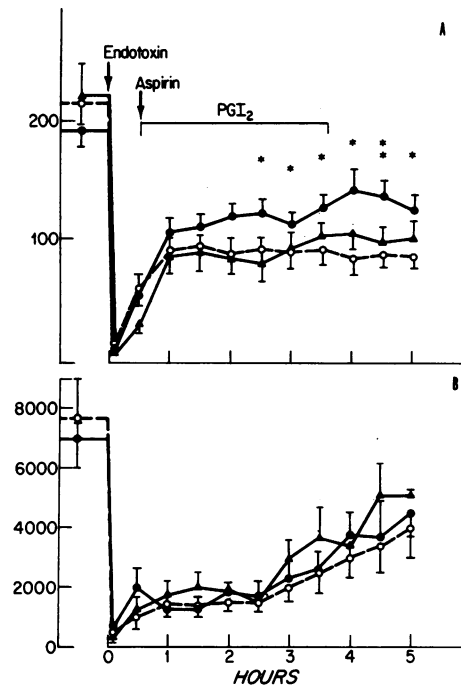*Catecholamines.* Norepinephrine levels in untreated controls increased threefold 6 min after endotoxin,

FIGURE 5 Blood platelet × 10³/mm³(A) and leukocytes/mm³(B) decreased following endotoxin. PGI₂ infusion was accompanied by an increase in circulating platelets which became significant after 2 h of infusion. Platelet levels in the aspirin group remained low and similar to controls. O, control; ●, PGI₂; ▲, aspirin; *, comparisons between PGI₂ and control animals.
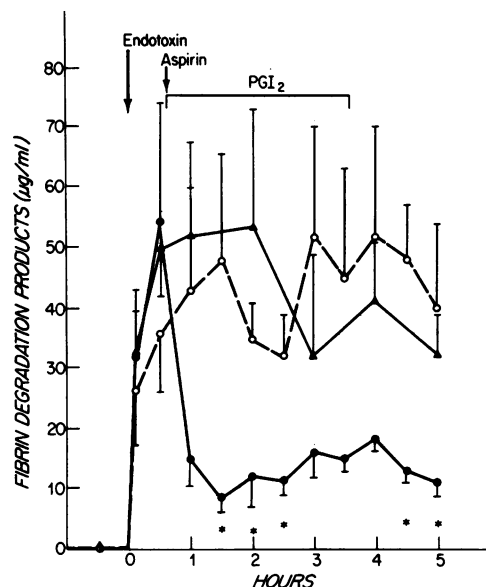

FIGURE 6 FDP rose following endotoxin and fell during the PGI₂ infusion. FDP in the aspirin group were not significantly different from the control group. O, control; ●, PGI₂; ▲, aspirin; *, comparisons between PGI₂ and control animals.
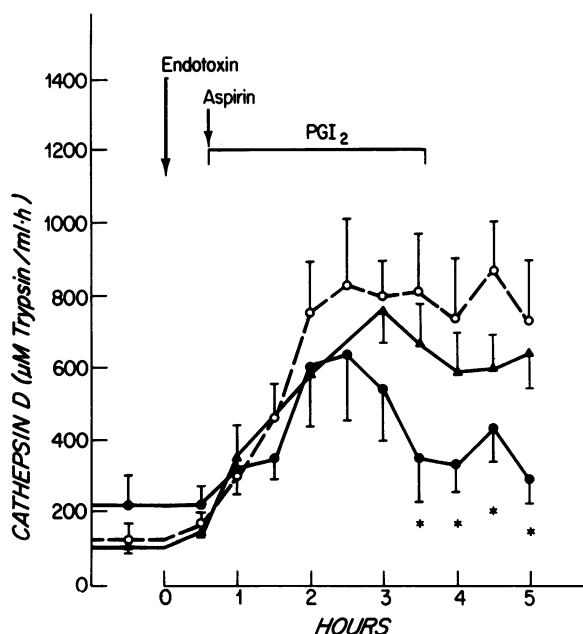
FIGURE 7 Plasma cathepsin D levels increased after endo-
toxin. The rise plateaued after 2.5 h and was unaffected by
aspirin. PGI_2 infusion was followed by a decrease in cathepsin
D to base line. O, control; ●, PGI_2; ▲, aspirin; *, comparisons
between PGI_2 and control animals.

FIGURE 8 Norepinephrine levels increased with endotoxin.
PGI_2 prevented a further increase noted in the controls and
eventually restored norepinephrine to base-line values. In
the aspirin group norepinephrine levels rose higher than
controls. O, controls; ●, PGI_2; ▲, aspirin; †, comparison
between aspirin and control animals; *, comparisons between
PGI_2 and control animals.

fivefold 2 h after endotoxin infusion, and remained
elevated during the remaining 3 h period ($P < 0.005$,
Fig. 8). Following PGI_2, arterial levels of norepineph-
rine were significantly lower and returned to base-line
values by 4 h. In the aspirin group norepinephrine
increased fivefold after 2 h and was significantly
higher than controls after 4 h ($P < 0.05$). Arterial
dopamine initially increased 6 min following endo-
toxin ($P < 0.005$), and remained elevated in all three
groups (Table I). Arterial epinephrine increased more
than sevenfold following endotoxin administration
($P < 0.01$). Neither PGI_2 nor aspirin had any significant
effect on epinephrine levels.

Survival. In order to maintain a stable hemoglobin
and pH, untreated control animals required 705±60
ml/h lactated Ringers solution and 10.0 ml/h bicar-
bonate; the PGI_2 group required 700±74 ml/h Ringers
and 10.2 ml/h bicarbonate; finally, after aspirin 633±64
ml/h Ringers and 10.0 ml/h bicarbonate were needed.
Watery diarrhea was observed in four control, three
PGI_2 treated and two aspirin treated animals. All eight
untreated dogs and six aspirin treated dogs died within
24 h following the administration of endotoxin. 9 out
of 10 PGI_2 treated animals survived more than 24 h
($P < 0.025$).

DISCUSSION

Lethal endotoxemia results in systemic hypotension,
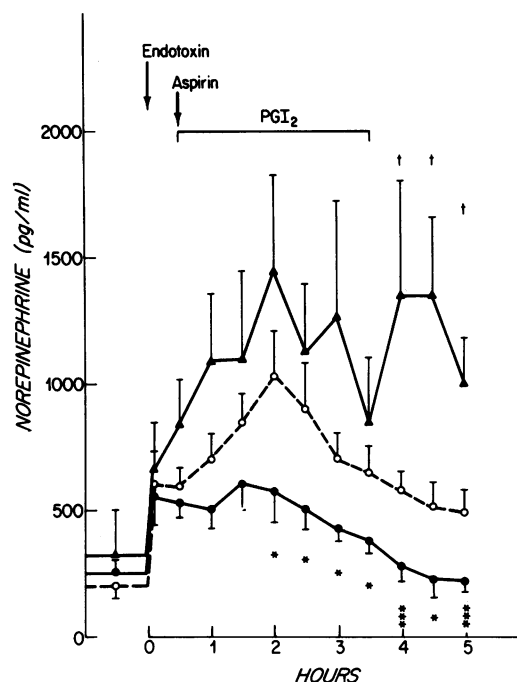transient pulmonary hypertension, and reduction in

cardiac output. Multiple organ failure develops: acute
respiratory failure leads to a rise in $\dot{Q}_S/\dot{Q}_T$; acute renal
failure is heralded by persistent severe oliguria;
hepatocellular dysfunction is manifest by elevation
of the serum enzymes glutamic-oxaloacetic trans-
aminase and glutamic-pyruvic transaminase as re-
ported by Wise et al. (16), as well as increases in the
acid hydrolase cathepsin D (17). These enzyme eleva-
tions are thought to be due to hepatocyte damage
with lysosomal disruption caused by leukocyte and
erythrocyte aggregates in hepatic sinusoids (18, 19).

Early and prominent hematologic abnormalities
are thrombocytopenia and leukopenia. Endotoxin is
known to cause platelet clumping (2). Platelet ag-
gregation and neutrophil stimulation by particulates
(20) lead to the generation of prostaglandins. The
high levels of thromboxane (Tx)B_2 the stable metabolite
of thromboxane A_2, within 30 min of the administra-
tion of endotoxin (16) is presumably a consequence
of the metabolic activities of platelets and leukocytes.
It is likely that TxA_2 is important in promoting
further platelet aggregation as well as in the mediation
of the cardiovascular abnormalities observed with
endotoxemia. The vasoconstrictive properties of TxA_2
can account for the early pulmonary hypertension

TABLE I
Plasma Catecholamine Concentrations

	Time after endotoxin							
	0	6 min	30 min	1 h	2 h	3 h	4 h	5 h
					pg/ml			
Norepinephrine								
Control	213±32	590±139	590±70	694±90	1,028±169	698±80	573±62	488±77
PGI₂	246±30	545±122	521±52	607±73	575±109*	439±37*	255±32‡	214±28‡
Aspirin	321±153	677±151	863±150	1,097±264	1,452±396	1,289±442	1,354±444§	996±165§
Dopamine								
Control	190±14	286±36	282±49	304±31	363±79	384±83	311±43	293±50
PGI₂	263±34	341±49	314±38	332±32	335±41	322±31	277±33	259±27
Aspirin	331±69	411±61	535±64	397±64	439±82	422±107	319±71	472±52
Epinephrine								
Control	273±139	2,291±971	1,143±471	1,269±428	1,296±468	1,310±293	1,139±600	499±238
PGI₂	238±84	1,290±468	782±229	826±179	897±298	‹ 756±700	353±145	296±142
Aspirin	132±34	1,405±480	2,007±605	1,226±468	1,393±556	1,098±548	1,042±322	1,035±215

* PGI₂ group compared with control animals. $P < 0.05$.
† PGI₂ group compared with control animals. $P < 0.005$.
§ Aspirin group compared with control animals. $P < 0.05$.

while negative inotropic properties of TxB₂ may explain in part the reduced flow (17, 21), although the levels of TxB₂ used in in vitro studies were far above anything which can be achieved in vivo. Pretreatment of animals with the cyclo-oxygenase inhibitors indomethacin (22) or ibuprofen (23) and thromboxane synthetase inhibitors, imidazole or 7-(1-imidazolyl)-hepatanoic acid ameliorated the severe thrombocytopenia following endotoxin (24) and prevented the rise of serum acid hydrolase activity of lysosomal origin (23). Furthermore, many other salutary effects were noted after pretreatment with these cyclo-oxygenase and thromboxane synthetase inhibitors including the maintenance of hepatic function and improved long term survival (16, 17, 22, 23). These beneficial effects required the prophylactic use of antagonists. In the present study, aspirin given 30 min after endotoxin did not reverse the fall in platelets, nor was there restoration of the rise in FDP and cathepsin D levels. Further, although MAP and MPAP rose, there was no increase in CI; PVR and SVR remained high and there was a fatal outcome.

Intravascular coagulation is a prominent event in endotoxemia. Its occurrence was signaled by the fall in platelets and fibrinogen, and the rise in FDP. It is likely that platelet aggregation and disseminated intravascular coagulation were triggered by the same stimulus since imidazole has been reported by Wise et al. (16) to prevent severe thrombocytopenia, as well as limit the rise in FDP. PGI₂ is known to inhibit platelet aggregation by causing an increase in cyclic AMP (25). Our observed rise in platelet counts follow-

ing PGI₂ and fall in FDP indicates the effectiveness of PGI₂ in reversing the intravascular coagulopathy.

Treatment of endotoxemia with PGI₂ significantly modified metabolic events, organ function and survival. We believe the mechanism relates directly to the ability of PGI₂ to stimulate cyclic AMP production. Thus, increases in platelet cyclic AMP prevents platelet aggregation, disseminated intravascular coagulation and the generation of negative inotropic agents such as TxB₂ (21). Our observations that aspirin was ineffective therapy argues that TxA₂ does not play an important role in the pathophysiology of endotoxemia, although it may be important in the development of increased V_D/V_T. The observed rise of cardiac output in response to PGI₂ is probably due, in part, to vasodilatation and reduction in SVR and cardiac afterload. The fact that neither the CVP nor PAWP changed makes alterations of venous return, venous capacitance, and/or compliance unlikely. Reversal by PGI₂ of flow limitations due to right ventricular failure secondary to pulmonary hypertension is also unlikely, in as much as PGI₂ had no appreciable effect on MPAP. It is possible that in addition to simulating cyclic AMP, the vasodilating effects of PGI₂, particularly with regard to the coronary vasculature (26) may have contributed to improved cardiac function.

The rapid reversal of cardiac dysfunction by PGI₂ contrasts with the slow reversal of renal failure and hepatocellular function reflected by urine flow and cathepsin D activity (Figs. 4, 7). These events may indicate improved cellular function secondary to the

improved perfusion. The delayed restoration of nor-epinephrine levels with PGI$_2$ may simply be a function of a slow reversal of the state of stress and the stimulus to production (Fig. 8). The selective reduction of norepinephrine and not dopamine or epinephrine may relate to a direct inhibition of norepinephrine release by PGI$_2$ from sympathetic nerve endings in blood vessels (27). It is also possible that endotoxin interfered with the pulmonary endothelial clearance of norepinephrine. Normally, 25% of circulating nor-epinephrine, but not epinephrine or dopamine, is extracted during passage through the lungs (28). PGI$_2$ may have restored normal pulmonary metabolic function.

Surprisingly, PGI$_2$ did not reverse $\dot{Q}_s/\dot{Q}_T$ during the 5-h observation period. An infusion of PGI$_2$ into animals made hypoxic with pulmonary emboli led to a lowering of $\dot{Q}_s/\dot{Q}_T$ within 15–30 min (8). The failure of PGI$_2$ to promptly reverse respiratory failure in endotoxemia where microemboli are thought to play a prominent role is unexpected (6) and suggests that microemboli, which may possibly have been formed in the lung, were not affected by PGI$_2$ during the limited 5-h period of observation. Studies in septic dogs and patients have shown that platelets and granulocytes are entrapped by the lungs (29, 30). However, these events correlate poorly with abnormalities in respiratory function. It is likely that other factors are involved in lung damage and the functional abnormalities of sepsis.

Leukocytes may mediate endothelial damage (31). Neutrophils contain neutral proteases such as collagenase, elastase, and cathepsin D. Following infusion of endotoxin the decrease in leukocyte count may be due to complement-activation and release of complement (C)3a and C5a which are chemotactic and result in sequestration of leukocytes in the micro-vasculature (29). During the process of neutrophil activation and degranulation, lysosomal contents may be discharged not only into phagocytic vascuoles within the cell, but may inadvertently escape into plasma (32). It is conceivable that other toxic oxygen derivatives such as superoxides are also released and cause endothelial cell damage. The natural defenses against these events are the circulating antiproteases and scavengers of superoxide anions.

The potential benefit of PGI$_2$ regarding leukocytes may be outweighed by its inhibitory actions on chemotaxis and the hexose monophosphate shunt (33). These inhibitory effects may be hazardous during a clinical setting of bacteremia where reticul-oendothelial function is important.

The mechanisms whereby PGI$_2$ modifies the response to endotoxemia remain obscure. The results of the current investigation provide evidence of hemato-logic, biochemical and cardiovascular activities of PGI$_2$ which coincide with improved survival.

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