

## Ibuprofen in canine endotoxin shock.

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*J Clin Invest.* 1982;70(3):536-541. <https://doi.org/10.1172/JCI110645>.

### Research Article

The participation of prostaglandins in the physiologic alterations of endotoxin shock has been well established with the aid of prostaglandin synthetase inhibitors. Our study was designed to investigate the potential of ibuprofen, a highly specific cyclooxygenase inhibitor, to reverse the hemodynamic and acid base abnormalities of canine endotoxin shock. Mean blood pressure fell to 49.8 +/- 6.6 mm Hg in dogs given endotoxin by 5 min after injection, and remained below 83 mm Hg for the duration of the 120-min observation period. In animals given endotoxin followed by ibuprofen, a similar initial drop of systemic blood pressure was seen, but it subsequently recovered to 150.2 +/- 4.1 mm Hg by 120 min (P less than 0.001). Cardiac index increased in animals given ibuprofen (2.3 +/- 0.28 liter/m<sup>2</sup> per min) compared with animals given endotoxin alone (1.0 +/- 0.09 liter/m<sup>2</sup> per min) by termination of the experiment. The arterial pH dropped in endotoxin treated animals to 7.18 +/- 0.03 by 120 min. Ibuprofen prevented the acidosis, the final pH in ibuprofen and endotoxin treated animals measuring 7.36 +/- 0.01. We conclude that ibuprofen protects against the hypotension, acidosis, and depression of cardiac index of canine endotoxin shock.

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# Ibuprofen in Canine Endotoxin Shock

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**ABSTRACT** The participation of prostaglandins in the physiologic alterations of endotoxin shock has been well established with the aid of prostaglandin synthetase inhibitors. Our study was designed to investigate the potential of ibuprofen, a highly specific cyclooxygenase inhibitor, to reverse the hemodynamic and acid base abnormalities of canine endotoxin shock. Mean blood pressure fell to  $49.8 \pm 6.6$  mm Hg in dogs given endotoxin by 5 min after injection, and remained below 83 mm Hg for the duration of the 120-min observation period. In animals given endotoxin followed by ibuprofen, a similar initial drop of systemic blood pressure was seen, but it subsequently recovered to  $150.2 \pm 4.1$  mm Hg by 120 min ( $P < 0.001$ ). Cardiac index increased in animals given ibuprofen ( $2.3 \pm 0.28$  liter/m<sup>2</sup> per min) compared with animals given endotoxin alone ( $1.0 \pm 0.09$  liter/m<sup>2</sup> per min) by termination of the experiment. The arterial pH dropped in endotoxin treated animals to  $7.18 \pm 0.03$  by 120 min. Ibuprofen prevented the acidosis, the final pH in ibuprofen and endotoxin treated animals measuring  $7.36 \pm 0.01$ . We conclude that ibuprofen protects against the hypotension, acidosis, and depression of cardiac index of canine endotoxin shock.

## INTRODUCTION

There is increasing evidence that prostaglandins are involved in various forms of acute injury. Prostaglandin (PG)<sup>1</sup> production is increased in endotoxin-induced injury in several species (1-4). Elevated levels of PGF<sub>2α</sub> have been demonstrated in patients with clinical sepsis (3). A correlation exists between (1) decreased levels of prostaglandins induced by prostaglandin synthesis inhibitors such as indomethacin or fatty acid deficiency, and (2) improved hemodynamics and survival in experimental endotoxin shock (4-7). These data

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Received for publication 14 December 1981 and in revised form 23 March 1982.

<sup>1</sup> Abbreviations used in this paper: PAP, pulmonary artery pressure; PG, prostaglandin; PGI<sub>2</sub>, prostacyclin; PMN, polymorphonuclear cells; P $\bar{V}$ O<sub>2</sub>, mixed venous oxygen tension; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance, V<sub>O</sub><sub>2</sub>, oxygen consumption.

have implicated prostaglandins as mediators of physiologic changes of endotoxin shock, though their mechanisms of action have not yet been established.

Concern about the therapeutic use of prostaglandin inhibitors has arisen. Indomethacin may accentuate the capillary permeability injury of endotoxin despite improved hemodynamics (8). Certain prostaglandins may increase the ability to withstand endotoxin. Specifically, PGI<sub>2</sub>, prostacyclin, appears to protect the lung against pulmonary hypertension and increased lymph flow characteristic of endotoxin-induced injury (9).

Ibuprofen (Motrin) is a reversible cyclooxygenase inhibitor with additional preferential inhibition of thromboxane synthesis (10).<sup>2</sup> Thromboxane, a potent vasoconstrictor which also enhances platelet aggregation, is elevated early in endotoxin induced injury and may mediate pulmonary hypertension. Ibuprofen appears to inhibit polymorphonuclear cell (PMN) and platelet aggregation. Both are important activities since they have been implicated as mediators of the pulmonary damage of sepsis and endotoxemia (11, 12).<sup>2</sup> In contrast to indomethacin, ibuprofen does not increase the capillary permeability injury of endotoxin or the chemotactic products of the lipoxygenase pathway (13). These factors suggest possible beneficial effects of ibuprofen in endotoxin shock. The purpose of this study was to test the ability of ibuprofen to influence physiologic changes of canine endotoxin shock.

## METHODS

Conditioned adult mongrel dogs weighing ~15 kg were anesthetized with pentobarbital sodium 35 mg/kg and paralyzed with pancuronium bromide 0.44 mg/kg i.v. Dogs were mechanically ventilated on room air via tracheostomy. The femoral artery was cannulated and a Swan-Ganz catheter was placed into the pulmonary artery from the femoral vein. Systemic and pulmonary artery pressures were recorded on a multichannel recorder. Cardiac output was measured by thermodilution (cardiac output computer model 9520-A, Edwards Laboratory). Mixed exhaled gas concentrations were determined by analyzing gas with a mass spec-

<sup>2</sup> Personal communication. Data on file with Upjohn Company.

trometer from a mixing chamber connected to the expiratory circuit of the ventilator. Blood gas determinations were measured on an IL 813 blood gas analyzer (Instrumentation Laboratories, Lexington, MA). Systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), oxygen consumption ( $\text{VO}_2$ ) and cardiac index were calculated by standard application of appropriate equations (14). Base-line measurements were repeated twice at least 20 min apart to ensure stability. After an injection of 0.9% NaCl or endotoxin at time ( $t$ ) = 0, all measurements were repeated at  $t$  = 5, 20, 60, 90, and 120 min.

Four groups of dogs were studied under the above standard protocol. Six control dogs (group I) received a sham injection of normal saline at  $t$  = 0. Six dogs (group II) received ibuprofen 25 mg/kg (Upjohn Co., Kalamazoo, MI) given intravenously over 1–2 min immediately before obtaining the first base-line values and a sham injection of saline at  $t$  = 0. Eight dogs received *Escherichia coli* endotoxin 2 mg/kg (Sigma Chemical Co., St. Louis, MO, serotype 0127:B8) i.v. at  $t$  = 0 (group III). Six dogs received *E. coli* endotoxin 2 mg/kg at  $t$  = 0 followed by ibuprofen 25 mg/kg at  $t$  = 5 (group IV). Six dogs received *E. coli* endotoxin 2 mg/kg at  $t$  = 0 followed by ibuprofen 25 mg/kg at  $t$  = 5 (group IV), the nadir of hypotension to approximate the hypotension of clinical endotoxin shock.

Statistical significance was evaluated using the two-tailed unpaired Student's  $t$  test to compare groups of dogs, and the paired  $t$  test to compare values at different times within a group (15). Values on graphs are expressed as means  $\pm$  standard error.

## RESULTS

Mean blood pressure remained stable in control animals, group I, and ibuprofen only animals, group II, throughout base line and observation periods (Fig. 1). In group III, animals given only endotoxin, blood pressure decreased to  $49.8 \pm 6.6$  within 5 min of endotoxin injection and remained below 83 mm Hg for the duration of the observation period. Group IV animals,

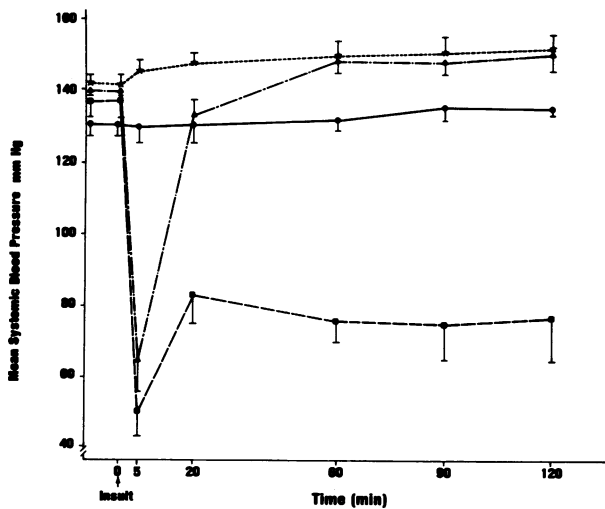


FIGURE 1 Mean blood pressure in group I, ●; group II, ★; group III, ■; and group IV, ▲ animals at time  $t$  = base line, 5, 20, 60, 90, and 120 min.

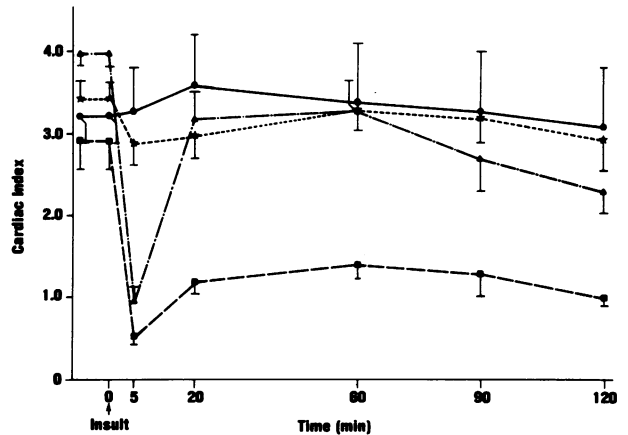


FIGURE 2 Mean cardiac index (liters per square meter per minute) in group I, ●; group II, ★; group III, ■; and group IV, ▲ dogs throughout base-line and experimental periods.

given ibuprofen 5 min after endotoxin, showed a similar initial drop in blood pressure with endotoxin injection but recovered at 20 min to  $133.2 \pm 4.1$  mm Hg ( $P < 0.001$ ), with all values from 20 min through termination of the experiment increased compared to those of animals given endotoxin alone. In group IV animals, observations were continued for 300 min after endotoxin injection, and blood pressure was maintained at  $158.2 \pm 5.2$  mm Hg.

Cardiac index similarly remained stable in group I and group II animals throughout the study (Fig. 2). Mean cardiac index in group III animals dropped to  $0.56 \pm 0.007$  liter/ $\text{m}^2$  per min by 5 min after endotoxin, recovered by 60 min to  $1.4 \pm 0.2$  liter/ $\text{m}^2$  per min, but subsequently deteriorated to  $1.0 \pm 0.09$  liter/ $\text{m}^2$  per min by 120 min. Group IV dogs showed an initial drop in cardiac output as in group III animals but recovered by 20 min to  $3.2 \pm 0.34$  liter/ $\text{m}^2$  per min ( $P < 0.001$ ) and remained improved throughout the study.

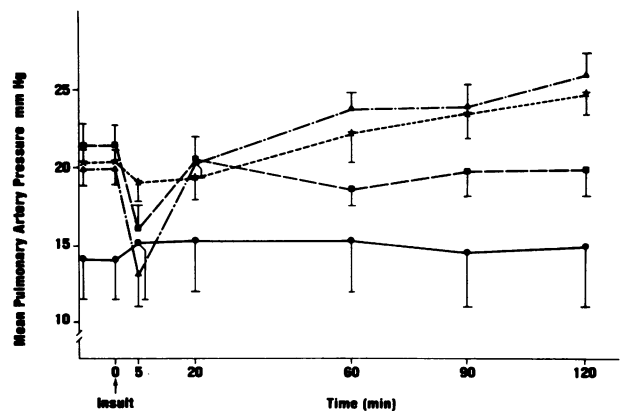


FIGURE 3 Mean PAP in group I, ●; group II, ★; group III, ■; and group IV, ▲ dogs through base-line and observation times.

TABLE I  
SVR, mm Hg/liter per min

	Time*					
	Base line	5 min	20 min	60 min	90 min	120 min
Group I	51.6±4.3	53.8±6.9	53.4±8.9	58.4±10.7	62.6±13.2	65.1±11.9
Group II	67.4±6.8	79.9±11.1	80.5±12.2	72.3±11.4	78.0±16.3	90.9±21.5
Group III	81.0±14.5	123.2±24.9	88.9±8.2	75.0±10.1	89.9±20.2	94.9±15.2
Group IV	62.2±4.1	105.6±12.6	73.0±8.4	80.6±13.3	101.1±17.9	114.4±15.9

\* Mean±SEM.

Pulmonary artery pressure (PAP) was stable in group I dogs but rose gradually throughout the experiment in group II dogs ( $P < 0.001$ ) (Fig. 3). PAP dropped in group III animals with endotoxin injection but returned to base line by 20 min. After an initial drop with endotoxin, PAP values of group IV animals returned to base-line values when ibuprofen was injected. PAP measurements at 60 and 120 min were significantly higher than those of group III dogs ( $P < 0.002$ ).

SVR and PVR showed no significant changes throughout base-line and observation periods in group I (Tables I and II). Group II animals showed a trend of increasing SVR and PVR from base-line values to 120 min, though increases were not statistically significant ( $P = 0.125$  and  $P = 0.056$ , respectively). SVR and PVR increased transiently with endotoxin injection in group III but returned to base line by 60 min with increasing values from this time until the end of the experiment. An early rise of SVR and PVR was also seen in group IV dogs with endotoxin injection with a subsequent return to base-line values by 20 min. From 20 min until termination of the experiment, both SVR and PVR rose in group IV animals. Differences in SVR and PVR between group III and group IV were not significant at any time.

Oxygen consumption,  $\dot{V}O_2$ , remained stable in control animals (Table III). Base-line values in group II animals were lower than those in group IV reflecting lower average body weight in group II (group II,  $\dot{V}O_2$

= 7.0 ml/kg per min vs. group III,  $\dot{V}O_2 = 6.8$  ml/kg per min). Oxygen consumption increased steadily throughout the experiment in group II dogs ( $P < 0.005$ ).  $\dot{V}O_2$  dropped with endotoxin administration in group III animals but returned to base line by 20 min.  $\dot{V}O_2$  also dropped in group IV animals with endotoxin but returned to base-line values with no difference at any time between group III and group IV values.

Arterial oxygen tension values ( $PaO_2$ ) remained stable throughout base-line and observation periods for all groups except for the control animals in which  $PaO_2$  rose slowly throughout the observation period and group IV animals in which  $PaO_2$  increased from  $83.9 \pm 1.5$  mm Hg to  $91.4 \pm 1.4$  mm Hg ( $P < 0.009$ ) (Table IV).

Mixed venous oxygen tension ( $P\bar{v}O_2$ ) did not change in groups I and II but fell with endotoxin administration in group III (Table V). This value returned to base line by 20 min in group III. The  $P\bar{v}O_2$  in group IV also dropped with endotoxin, but returned to base line as in group III, with no difference between groups III and IV values from 20 min through termination of the experiment.

Arterial pH remained stable in groups I and II throughout base line and observation periods (Fig. 4). After a slight initial rise, the pH in group III fell gradually to  $7.18 \pm 0.03$  at the termination of the study. Group IV animals showed an initial drop in pH at 20 min after endotoxin, but pH returned to  $7.36 \pm 0.01$  by the termination of the experiment ( $P < 0.001$ ).

TABLE II  
PVR, mm Hg/liter per min

	Time*					
	Base line	5 min	20 min	60 min	90 min	120 min
Group I	2.6±0.15	5.3±2.0	5.1±2.3	5.8±2.4	6.6±3.1	6.0±3.1
Group II	5.3±0.96	5.7±1.5	5.8±1.8	6.5±1.6	7.7±2.4	9.8±3.2
Group III	4.6±0.5	19.1±5.3	11.3±2.2	8.7±1.7	9.0±2.1	11.8±0.48
Group IV	4.3±0.36	11.1±2.3	6.5±0.93	8.3±1.4	10.1±1.6	14.0±2.3

\* Mean±SEM.

TABLE III  
Oxygen Consumption, ml/min

	Time*					
	Base line	5 min	20 min	60 min	90 min	120 min
Group I	103.6±10.6	99.5±15.3	102.5±15.1	110.6±20.6	104.1±18.3	114.9±25.7
Group II	88.5±7.7	92.2±10.4	89.8±8.9	94.5±9.9	98.7±9.8	110.1±9.5
Group III	106.7±9.1	57.8±12.8	104.1±12.6	103.2±13.2	103.0±14.8	100.2±13.7
Group IV	116.0±12.6	69.9±11.7	117.6±8.4	124.7±13.7	112.5±12.8	117.5±12.2

\* Mean±SEM.

## DISCUSSION

Several mediators such as complement,  $\beta$ -endorphins, and serotonin (16–18) have been postulated as fundamental to the pathophysiologic changes of septic shock. Prostaglandins, ubiquitous vasoactive products of the arachadonic acid cascade, are elevated in experimental endotoxin shock (1–3, 19). Fletcher and Ramwell in an experimental model evaluated the use of indomethacin and aspirin and found that prostaglandin levels were elevated within 1–2 min of endotoxin injection. This elevation coincided with hemodynamic deterioration. Both aspirin and indomethacin ameliorated hemodynamic changes of endotoxin and decreased prostaglandin  $F_{2\alpha}$ , though animals that died in the group treated with endotoxin alone did not have significantly different levels of prostaglandins than survivors. These findings suggested that some property other than prostaglandin inhibition accounted for improved survival in this model (20, 21). Inhibitors of the cyclooxygenase pathway, such as indomethacin, may shunt arachidonic acid metabolites into the alternative lipoxygenase pathway with increased synthesis of chemotactic leukotrienes (22). Higgs et al. (13) showed increased leukocyte chemotaxis with indomethacin in some forms of inflammation, and Ogletree et al. (8) described pulmonary injury associated with increased capillary permeability with indomethacin in endotoxemia. Further, several of the prostaglandins, specifically  $PGE_1$  and  $PGI_2$ , are known to vasodilate, diminish vascular resistance, and

prevent leukocyte aggregation and lysosomal enzyme release, all properties that would afford a protective effect against pulmonary injury (23, 24). Demling et al. (9) have demonstrated diminished pulmonary injury with prostacyclin infusion in sheep. Finally, drugs such as acetylsalicylic acid and indomethacin have so wide a spectrum of biologic activities that the improved hemodynamics in experimental models can only be supposed to be related to prostaglandin inhibition.

Ibuprofen, in contrast, has several potential advantages over other antiinflammatory agents utilized in experimental endotoxin shock. It is a reversible, short-acting, cyclooxygenase inhibitor with preferential blocking of thromboxane synthesis (10).<sup>2</sup> Ibuprofen has few potentially deleterious "side effects" such as phospholipase inhibition and stimulation of slow-reacting substance of anaphylaxis production.<sup>2</sup> It does not increase metabolites of the lipoxygenase pathway (13). Ibuprofen stabilizes lysosomal membranes, retards release of cathepsin D and  $\beta$ -glucuronidase, and inhibits peroxidation in rat liver (25, 26). It totally suppresses zymogen-induced lysozyme release from granulocytes, whereas no such suppressant activity was observed with aspirin and only moderate suppression was noted with indomethacin (27). Ibuprofen also inhibits migration of leukocytes in vitro using glass capillary tubes in a dose-dependent fashion (28). Baboons with coronary artery ligation pre- and posttreated with ibuprofen had markedly diminished PMN infiltration of

TABLE IV  
 $PaO_2$ , mm Hg

	Time*					
	Base line	5 min	20 min	60 min	90 min	120 min
Group I	93.2±2.4	96.0±1.9	95.8±2.2	101.8±3.9	101.5±5.0	105.8±7.3
Group II	89.4±2.7	92.6±2.6	92.6±2.5	97.2±2.4	95.6±3.7	93.3±6.4
Group III	88.1±2.2	96.7±6.9	79.6±5.8	78.2±5.7	79.5±5.4	80.8±5.2
Group IV	84.0±1.5	88.0±8.8	87.5±4.5	93.2±2.8	92.2±2.8	91.4±1.4

\* Mean±SEM.

TABLE V  
Mixed Venous  $P\bar{v}O_2$ , mm Hg

	Time*					
	Base line	5 min	20 min	60 min	90 min	120 min
Group I	43.9±1.6	41.7±2.6	42.5±2.5	43.1±2.5	40.1±3.2	38.8±3.2
Group II	43.1±1.0	41.1±1.6	41.0±2.2	45.2±1.8	43.6±2.4	41.7±3.0
Group III	43.8±0.8	24.2±1.8	31.0±1.8	41.0±2.8	40.9±2.3	40.6±3.2
Group IV	47.4±1.0	28.6±3.2	42.1±1.6	49.4±1.8	45.8±2.0	43.6±1.4

\* Mean±SEM.

the myocardium compared with controls.<sup>3</sup> Finally, ibuprofen inhibits platelet aggregation induced by ADP, thrombin, epinephrine, collagen, and arachidonic acid. Platelet activating factor induced platelet aggregation that is not blocked by aspirin or indomethacin is inhibited by ibuprofen (29).

These data show that treatment with ibuprofen reversed the detrimental changes in blood pressure, cardiac output, and arterial pH in canine endotoxin shock. Though there were some trends, SVR and PVR  $\dot{V}O_2$ ,  $P\bar{v}O_2$ , and  $PaO_2$  were not altered in ibuprofen-treated animals compared with animals treated with endotoxin alone. PAP tended to be higher in animals posttreated with ibuprofen than those treated with endotoxin alone; the difference between these values became significant by termination of the experiment. Ibuprofen alone caused no significant changes from base line over the observation period except increased PAP. Perhaps this effect may be explained by inhibition of vasodilator prostaglandins by ibuprofen, an effect previously observed with ibuprofen in doses that inhibit in vitro platelet aggregation (30).

The mechanism of the protective effect of ibuprofen in endotoxemia is not clear. Endotoxin is known to

cause margination of leukocytes, thickening of endothelial cells, and the formation of thrombi in the small veins in the peripheral circulation as well as lysosomal enzyme release (31, 32). An endotoxin shock-induced inotropic disorder has been well documented, with evidence that this myocardial dysfunction is associated with depressed, membrane bound calcium-stimulated ATPase activity (33, 34). Ibuprofen reduces inflammation and lung lymph flow in endotoxin-induced injury, both actions presumed secondary to prostaglandin inhibition and membrane stabilization (10, 22). Data from our lab (unpublished observations) suggest an improved myocardial inotropic state with ibuprofen in endotoxemia. The improved blood pressure, cardiac output, and arterial pH observed in this study may reflect improved vascular integrity and peripheral circulation with ibuprofen in endotoxemia, an action that might be explained by inhibition of thromboxane and  $PGF_{2\alpha}$ . The source of prostaglandins responsible for the hemodynamic derangements of endotoxemia is unknown at this time, with leukocytes, platelets, and vascular endothelium all remaining potential candidates. Alternative explanations would be favorable action of ibuprofen on platelet aggregation or leukocyte migration as previously described.

Several questions remain unanswered by this study. The interrelationship between prostaglandins and other mediators such as bradykinin, complement, endorphins, and leukotrienes remains unexplored. The exact relationship of an experimental model of endotoxin shock injury to clinical sepsis has not been established. The question of improved survival in shock-like states with ibuprofen awaits further study.

#### ACKNOWLEDGMENTS

The authors wish to thank Karl Landberg for his technical assistance and the Upjohn Company for donation of the ibuprofen used in this study.

This work was supported by National Institutes of Health Academic Career Award IK07 HL0051801 and the Arkansas Lung Association.

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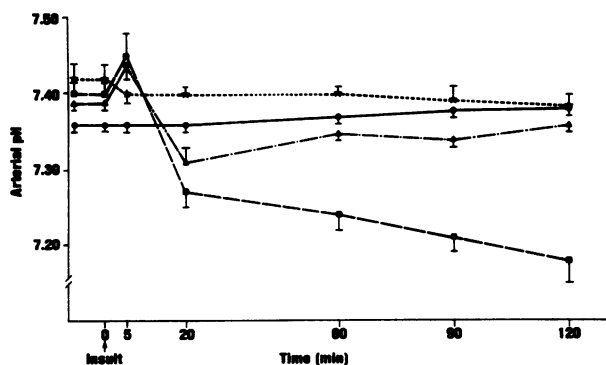


FIGURE 4 Arterial pH from femoral arterial line in group I, ●; group II, ★; group III, ■; and group IV, ▲ dogs at base line and designated times during observation period.

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