Effect of Indomethacin on Proteolysis in Septic Muscle

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The effect of indomethacin on protein degradation in skeletal muscle from septic rats was investigated. Sepsis was induced by cecal ligation and puncture (CLP). Control rats were sham-operated. Protein degradation rate was estimated by measuring release of tyrosine from incubated soleus (SOL) and extensor digitorum longus (EDL) muscles. Three experiments were performed. In the first experiment, indomethacin was administered subcutaneously (3 mg/kg) at the time of CLP and again after 3 hours. Control rats received corresponding volumes of solvent. Groups of rats were studied after 8 hours (early sepsis) or 16 hours (late sepsis). In the second experiment, the animals were pretreated 45 minutes before induction of sepsis with indomethacin (3 mg/kg) and again 3 hours after CLP and were studied during early sepsis. In the third experiment, indomethacin was added *in vitro* (3 μM) to incubated normal or septic muscle or to normal muscle incubated in the presence of plasma from septic animals, and release of prostaglandin E_2 (PGE_2) by incubated muscle was measured in addition to protein degradation. There was no mortality in early sepsis. Survival rate 16 hours after CLP was 8/16 (50%) in rats receiving control injections and 7/15 (47%) in indomethacin-treated rats (NS). Proteolytic rate in incubated EDL and SOL was increased by 20–25% during early sepsis and by 30–50% during late sepsis. The increased proteolytic rate was not affected by administration of indomethacin, neither in the first nor in the second experiment. When indomethacin was added *in vitro*, release of PGE_2 by septic muscles and by normal muscles incubated in the presence of septic plasma was reduced by about 50%, but the increased proteolytic rate in these muscles was not affected. In normal muscle, neither release of PGE_2 nor protein degradation was affected by indomethacin *in vitro*. The present results do not support a role for prostaglandins in the enhancement of muscle proteolysis during sepsis. Since neither survival rate nor protein breakdown was affected by indomethacin, recent suggestions to use this substance in the treatment of septic patients might be questioned.

ACCELERATED PROTEIN BREAKDOWN in skeletal muscle is well established in trauma and sepsis.[1-3] A role of prostaglandins for enhanced proteolysis in muscle tissue was suggested recently, for when arachidonic acid or prostaglandin E_2 (PGE_2) was added to incubated muscles from rats, protein breakdown increased by about 20%.[4]

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Submitted for publication: April 4, 1985.

In subsequent reports, it was suggested that the signal for enhanced protein degradation in trauma and sepsis is leukocytic pyrogen[5] or a degradative product of that substance.[6] Leukocytic pyrogen induces increased production of PGE_2 in various tissues, including muscle.[5] As a consequence of possible prostaglandin-mediated protein breakdown, the use of indomethacin or other cyclooxygenase inhibitors was suggested for the treatment of protein loss following injury and sepsis.[5-7]

The purpose of the present study was two-fold. First, we studied the effect of indomethacin, administered *in vivo*, on protein breakdown in skeletal muscle during sepsis in rats. Second, the effect of indomethacin added *in vitro* to incubated muscles from normal and septic animals was investigated.

Materials and Methods

Young male Sprague-Dawley rats weighing 60–70 g were used. Small animals were used since their soleus (SOL) and extensor digitorum longus (EDL) muscles are thin, facilitating adequate tissue oxygenation under *in vitro* incubation conditions.[8] Sepsis was induced in nonfasted rats by cecal ligation and puncture (CLP), as described previously.[9,10] Control animals were sham-operated. Saline solution, 5 cc/100 g body weight (bw), was injected subcutaneously on the back for hydration. The animals were allowed water but no food after the operative procedures. Groups of rats were used 8 hours (early sepsis) or 16 hours (late sepsis) after CLP or sham-operation, since the conditions of the rats at these time points was suggested previously to resemble human hypermetabolic and hypometabolic sepsis, respectively.[9,10] When the effects of indomethacin administered *in vivo* were studied (see below), the experiments were block designed, that is, an equal number of animals was included in the different experimental groups each time the experiments were performed.

TABLE 1. *Body Temperature, Hematocrit, Plasma Glucose, and Lactate in Experiments in Which Indomethacin (3 mg/kg) Was Given at the Time of CLP and After 3 Hours*

	Early Sepsis			Late Sepsis		
	Control (9)	CLP (9)	CLP + INDO (9)	Control (8)	CLP (8)	CLP + INDO (7)
Body temperature (°C)	38.1 ± 0.2	36.1 ± 0.4†	37.7 ± 0.3§	37.4 ± 0.2	35.2 ± 0.8*	33.6 ± 0.5†
Hematocrit (%)	37 ± 1	40 ± 1†	38 ± 1	38 ± 1	38 ± 2	41 ± 4
Glucose (mg/dl)	185 ± 4	142 ± 6†	127 ± 6†‡	88 ± 6	65 ± 5†	71 ± 4*
Lactate (mg/dl)	32 ± 1	28 ± 2	28 ± 2	25 ± 1	36 ± 6*	44 ± 7†

INDO = indomethacin. Numbers in parentheses indicate number of animals.
* $p < 0.05$; † $p < 0.01$ *vs.* control; ‡ $p < 0.05$; § $p < 0.01$ *vs.* CLP.

For the study of protein degradation, the EDL and SOL muscles were dissected with intact tendons under ether anesthesia, weighed, and incubated as described below. Blood was drawn by heart puncture for measurement of amino acids, glucose, lactate, and hematocrit. Body temperature was measured with a rectal probe.

Three experiments were performed. In the first experiment, indomethacin (3 mg/kg bw dissolved in 1 ml/kg of 0.1 M sodium bicarbonate) was administered subcutaneously at the time of CLP and again after 3 hours. Corresponding volumes of sodium bicarbonate were administered at the same time points to another group of rats undergoing CLP and to sham-operated control rats. Groups of rats were studied after 8 or 16 hours. In the second experiment, the same amount of indomethacin or solvent was administered intraperitoneally 45 minutes before and subcutaneously 3 hours after CLP. Rats in this experiment were studied only during early sepsis.

In the third experiment, indomethacin was added *in vitro* (3 μM) to incubated SOL muscles from unoperated, nonfasted rats (normal muscles) or from rats during late sepsis (septic muscles). In some experiments, normal muscles were incubated in the presence of septic plasma, as described previously by Clowes et al.,[6] that is, 0.25 ml of plasma from rats in late sepsis was added to 2.75 ml of incubation medium (see below). Indomethacin was dissolved in 50% ethanol before it was added *in vitro*. A corresponding volume of ethanol (10μl/ml) was added to incubation flasks containing control muscles. Contralateral muscle from the same animal always served as control.

The National Research Council's guide for the care and use of laboratory animals was followed in all experiments.

Protein Degradation

Muscles were preincubated for 30 minutes in 3 ml of a medium consisting of Krebs-Henseleit bicarbonate buffer (pH 7.4) supplemented with 10 mM glucose. The incubation medium was saturated with O_2:CO_2 (95:5) and incubation was performed at 37 C in a shaking water bath. After preincubation, the muscles were blotted gently on filter paper and transferred to 3 ml of fresh medium containing cycloheximide (0.5 mM). Rate of protein degradation was estimated by measuring the release of tyrosine into the incubation medium as described previously.[11,12] Tyrosine was determined according to Waalkes and Udenfriend.[13] Tissue concentration of free tyrosine, determined as described previously,[11] remained constant during incubation, both in control and septic muscles, thus making it possible to estimate protein degradation rate by measuring release of tyrosine into incubation medium.

Prostaglandin E_2

PGE_2 production by incubated muscle was determined by radioimmunoassay of PGE_2 that was released into the medium, as described previously.[4,5]

Plasma Glucose, Lactate, and Amino Acids

A YSI Model 23A glucose and lactate analyzer (Yellow Springs Instrument Co., Yellow Springs, Ohio) was used for enzymatic determination of glucose and lactate levels in plasma. For determination of amino acids, plasma was deproteinized in 5% sulfosalicylic acid and measurements were carried out using a Beckman 121-MB amino acid analyzer (Beckman Instruments, Inc., Palo Alto, CA).

Statistics

Results are given as mean ± SEM. Wilcoxon's nonparametric test for paired differences[14] or ANOVA was used for statistical comparisons when appropriate.

Results

There was no mortality among sham-operated rats or septic rats 8 hours after CLP. The survival rate 16 hours after CLP was 8/16 (50%). The corresponding figure for septic rats treated with indomethacin was 7/15 (47%) (NS).

Body temperature, hematocrit, plasma glucose and lactate in the first experiment are shown in Table 1. Re-

duced body temperature both in early and late sepsis, hypoglycemia and increased lactate in plasma during late sepsis are in agreement with a recent report from our laboratory.[15] Indomethacin prevented the reduction of body temperature during early sepsis and reduced blood glucose in the same group of animals.

Protein degradation rate was increased by 21% in EDL and by 25% in SOL muscle during early sepsis (Table 2). During late sepsis, the proteolytic rate was increased by 59% in EDL and by 28% in SOL (Table 2). Similar results were reported recently.[15] Protein breakdown was increased also in septic animals treated with indomethacin and the proteolytic rate was not significantly affected by indomethacin in any of the muscles during early or late sepsis (Table 2).

Total plasma amino acid concentrations were reduced in septic animals whether or not they were treated with indomethacin (Table 3). The plasma amino acid pattern became increasingly deranged during the septic course, and in late sepsis all except four amino acids (glutamine, alanine, leucine, and histidine) were significantly altered in septic rats. Almost all changes in individual amino acid concentrations in septic rats were present also in rats treated with indomethacin (Table 3).

In the second experiment also, indomethacin prevented the fall in body temperature and reduced blood glucose during early sepsis (Table 4). The stimulation of protein breakdown in EDL and SOL was somewhat less pronounced in septic rats treated with indomethacin than in untreated septic rats, but there were no significant differences in proteolytic rate between the two groups of septic animals (Table 5).

As in the first experiment, changes in plasma amino acid concentrations in septic rats were present also if the animals were pretreated with indomethacin (Table 6). In addition, some amino acids (valine, leucine, isoleucine,

TABLE 2. *Protein Degradation (μmol tyr × gww^{-1} × 2 h^{-1}) During Early and Late Sepsis in Experiments in Which Indomethacin (3 mg/kg) Was Administered at the Time of CLP and After 3 Hours*

	Control	CLP	CLP + Indomethacin
Early sepsis			
EDL	0.326 ± 0.010 (9)	0.393 ± 0.019† (9)	0.369 ± 0.021* (9)
SOL	0.376 ± 0.016 (9)	0.471 ± 0.025* (9)	0.402 ± 0.031 (9)
Late sepsis			
EDL	0.422 ± 0.022 (8)	0.669 ± 0.021† (8)	0.706 ± 0.016† (7)
SOL	0.477 ± 0.018 (8)	0.611 ± 0.027† (8)	0.604 ± 0.016† (7)

* $p < 0.05$; † $p < 0.01$ *vs.* control.
Numbers in parentheses indicate number of animals.

TABLE 3. *Plasma Amino Acids (μmol/L) in Experiments in Which Indomethacin (3 mg/kg) Was Given at the Time of CLP and After 3 Hours*

	Early Sepsis			Late Sepsis		
	Control (9)	CLP (9)	CLP + INDO (9)	Control (8)	CLP (8)	CLP + INDO (7)
Asp	20 ± 2	25 ± 4	18 ± 3	17 ± 1	24 ± 2*	23 ± 2*
Hpr	41 ± 2	26 ± 2†	28 ± 2†	40 ± 3	16 ± 2†	16 ± 1†
Thr	143 ± 9	127 ± 10	103 ± 4	247 ± 16	146 ± 10†	149 ± 9†
Ser	213 ± 15	162 ± 14*	137 ± 5†	275 ± 14	153 ± 4†	157 ± 7†
Asn	46 ± 4	29 ± 1†	27 ± 2†	51 ± 4	34 ± 1†	32 ± 3†
Glu	76 ± 3	70 ± 6	61 ± 4†	62 ± 3	153 ± 17†	162 ± 21†
Gln	545 ± 37	399 ± 33*	482 ± 26	504 ± 21	433 ± 39	339 ± 36†
Pro	133 ± 10	64 ± 3†	62 ± 4†	133 ± 6	61 ± 5†	70 ± 6†
Gly	367 ± 32	371 ± 27	321 ± 10	511 ± 18	321 ± 19†	300 ± 10†
Ala	409 ± 40	218 ± 14†	206 ± 19†	255 ± 17	215 ± 19	355 ± 80
Cit	101 ± 11	99 ± 5	87 ± 7	126 ± 13	68 ± 5†	101 ± 12‡
Val	125 ± 4	143 ± 16	107 ± 7	167 ± 8	131 ± 10*	127 ± 10*
Met	46 ± 2	28 ± 1†	26 ± 2†	46 ± 2	33 ± 1†	38 ± 1†
Ile	66 ± 4	66 ± 6	52 ± 4	100 ± 5	72 ± 5†	67 ± 5†
Leu	104 ± 9	126 ± 10	92 ± 7	148 ± 7	135 ± 10	135 ± 10
Tyr	51 ± 2	55 ± 3	41 ± 2†§	57 ± 4	45 ± 2*	50 ± 4
Phe	72 ± 4	88 ± 8	62 ± 3	57 ± 2	77 ± 3†	85 ± 3†
Try	46 ± 3	52 ± 4	43 ± 5	35 ± 3	21 ± 1†	22 ± 2†
Orn	49 ± 3	50 ± 6	44 ± 5	63 ± 8	87 ± 13*	109 ± 17*
Lys	260 ± 14	261 ± 16	238 ± 17	468 ± 27	310 ± 17†	362 ± 44*
His	77 ± 4	85 ± 2	73 ± 2	65 ± 2	74 ± 4	90 ± 5†
Arg	97 ± 5	81 ± 5†	69 ± 5†	109 ± 7	42 ± 11†	33 ± 10†
Total AA	3090 ± 130	2627 ± 98*	2380 ± 69†	3421 ± 173	2642 ± 67†	2819 ± 203*

INDO = indomethacin.
* $p < 0.05$; † $p < 0.01$ *vs.* control; ‡ $p < 0.05$; § $p < 0.01$ *vs.* CLP.
Numbers in parentheses indicate number of animals.

TABLE 4. *Body Temperature, Hematocrit, Plasma Glucose, and Lactate in Experiments in Which Indomethacin (3 mg/kg) Was Given 45 min before and 3 hours after CLP*

	Control (6)	CLP (6)	CLP + INDO (6)
Body temperature (°C)	38.4 ± 0.2	36.6 ± 0.4*	37.8 ± 0.2†
Hematocrit (%)	38 ± 1	41 ± 3	39 ± 3
Glucose (mg/dl)	170 ± 5	126 ± 10*	93 ± 6*†
Lactate (mg/dl)	32 ± 1	34 ± 2	38 ± 4

INDO = indomethacin.
* $p < 0.01$ *vs.* control; †$p < 0.05$ *vs.* CLP.
Numbers in parentheses indicate number of animals.

and tyrosine) were significantly altered only in the indomethacin-treated group in this experiment.

When indomethacin was added *in vitro* to incubated normal muscles, protein degradation and prostaglandin release were not altered (Table 7). The increased proteolytic rate in septic muscles and in normal muscles incubated in the presence of plasma from septic rats was also unaffected by indomethacin. Release of PGE_2 from these muscles, however, was reduced by about 50% (Table 7).

Discussion

The sepsis model used in the present study was suggested previously to duplicate the stages characteristic of sepsis in humans—an early hypermetabolic and a late hypometabolic state.[9,10] The metabolic alterations demonstrated 8 and 16 hours after CLP in the current investigation are in line with a recent report from this laboratory.[15] Hypothermia, hypoglycemia, and increased blood lactate indicate that the animals were in a hypometabolic state 16 hours after CLP, while unchanged lactate and near-normal blood glucose 8 hours after CLP are consistent with a hypermetabolic stage of sepsis.[16,17] In contrast to hypermetabolic sepsis in humans, hypothermia was present also during early sepsis in the present study.

In accordance with a previous study,[15] protein breakdown was enhanced in both the red soleus and the white EDL muscle during early sepsis and was further increased in late sepsis. Thus, the present experimental model, which is simple and clinically relevant,[10] seems to induce reproducible changes in muscle protein breakdown.

Interpretation of changes in plasma amino acid concentrations is difficult since they represent the sum effect of different factors affecting amino acid flux.[18] Total amino acid concentration in plasma was decreased following CLP in the present study. Reduced total amino acids were reported previously following different types of trauma and sepsis, probably in part reflecting enhanced

TABLE 5. *Protein Degradation (μmol tyr × gww^{-1} × 2 h^{-1}) During Early Sepsis in Experiments in Which Indomethacin (3 mg/kg) Was Given 45 Minutes Before and 3 Hours After CLP*

	Control (6)	CLP (6)	CLP + INDO (6)
EDL	0.329 ± 0.023	0.415 ± 0.041*	0.375 ± 0.024
SOL	0.345 ± 0.034	0.476 ± 0.034*	0.425 ± 0.026*

INDO = indomethacin.
* $p < 0.05$ *vs.* control.
Numbers in parentheses indicate number of animals.

TABLE 6. *Plasma Amino Acids (μmol/L) in Experiments in Which Indomethacin (3 mg/kg) Was Given 45 Minutes Before and 3 Hours After CLP*

	Control (6)	CLP (6)	CLP + INDO (5)
Asp	19 ± 3	18 ± 2	16 ± 2
Hpr	37 ± 2	33 ± 2	35 ± 0
Thr	150 ± 10	156 ± 21	146 ± 14
Ser	199 ± 13	172 ± 20	165 ± 14
Asn	44 ± 6	39 ± 4	40 ± 4
Glu	54 ± 5	56 ± 9	56 ± 6
Gln	541 ± 18	423 ± 35*	457 ± 26*
Pro	116 ± 10	74 ± 6†	76 ± 8*
Gly	341 ± 26	302 ± 22	317 ± 20
Ala	308 ± 32	189 ± 18†	217 ± 22*
Cit	84 ± 4	69 ± 6	78 ± 7
Val	134 ± 9	198 ± 34	208 ± 22†
Met	36 ± 1	22 ± 2†	24 ± 2†
Ile	73 ± 4	108 ± 16	111 ± 8†
Leu	124 ± 8	190 ± 28	200 ± 12†
Tyr	41 ± 2	48 ± 4	52 ± 2†
Phe	68 ± 3	70 ± 4	67 ± 2
Try	62 ± 5	53 ± 4	54 ± 3
Orn	35 ± 2	41 ± 7	40 ± 1
Lys	289 ± 16	273 ± 24	256 ± 25
His	68 ± 1	78 ± 6	79 ± 4*
Arg	79 ± 3	66 ± 4*	78 ± 4
Total AA	2901 ± 109	2679 ± 239	2771 ± 128

INDO = indomethacin; AA = amino acids.
* $p < 0.05$; †$p < 0.01$ *vs.* control.
Numbers in parentheses indicate number of animals.

TABLE 7. *Release of Tyrosine (μmol × gww^{-1} × $2h^{-1}$) and PGE_2 (ng × gww^{-1} × $2h^{-1}$) from Soleus Muscle, Incubated in the Absence or Presence of Indomethacin (3 μM)*

	Indomethacin	Tyr Release	PGE_2 Release
Normal muscle (7)	−	0.476 ± 0.032	13.1 ± 0.76
	+	0.440 ± 0.020	10.5 ± 1.01
Septic muscle (8)	−	0.706 ± 0.034	24.4 ± 6.23
	+	0.749 ± 0.041	12.1 ± 1.74†
Normal muscle plus septic plasma (7)	−	0.790 ± 0.045	14.5 ± 2.65
	+	0.789 ± 0.042	6.9 ± 2.08*

* $p < 0.05$; †$p < 0.01$ *vs.* muscle incubated without indomethacin.
Numbers in parentheses indicate number of paired observations.

amino acid uptake by the liver.[15,19-21] Despite reduced total amino acids, some individual amino acids were elevated during sepsis. In a previous study, phenylalanine, histidine, glutamate, and ornithine were increased in septic rats in a fashion parallel to accelerated protein breakdown, that is, during both early and late sepsis, and a significant positive correlation between proteolytic rate in EDL and SOL and plasma concentration of these amino acids was found.[15] In contrast, these amino acids were elevated only during late sepsis in the present study.

One signal for accelerated muscle proteolysis in sepsis is probably leukocytic pyrogen (interleukin-1)[5] or a degradative fragment of that substance.[6] Leukocytic pyrogen, which is a protein released by leukocytes, stimulates production of PGE_2 in various tissues, including muscle.[5,7] When PGE_2 was added to incubated normal rat muscles, protein breakdown was increased.[4] From these observations and others demonstrating increased prostaglandin synthesis and/or release during sepsis,[22,23] a role of prostaglandins for accelerated muscle proteolysis in trauma and sepsis was suggested. Consequently, the use of indomethacin or other cyclooxygenase inhibitors was proposed for the treatment of protein loss in these conditions.[5,7] In fact, accelerated proteolysis caused by arachidonic acid added to incubated normal muscles was abolished by indomethacin.[4] The effect of indomethacin on accelerated proteolysis in septic muscle, however, has not been previously elucidated.

In the first experiment of the present study, indomethacin was administered at the time of CLP and again after 3 hours. The results showed that protein degradation in EDL and SOL during sepsis was not significantly affected by this treatment. Also, the changes in plasma amino acid concentrations were unaffected by indomethacin.

In some previous reports, indomethacin was administered before induction of sepsis, since prostaglandin synthesis is increased early in the septic course.[22,24,25] Thus, the ineffectiveness of indomethacin in our first experiment could be due to too late an administration of the drug. Therefore, in the second experiment, we gave the first dose of indomethacin 45 minutes before CLP. The results of this experiment were similar to those of the first experiment, that is, the enhanced muscle proteolytic rate during sepsis was not significantly affected by indomethacin, and changes in plasma amino acids were not prevented by the treatment. In fact, some changes in plasma amino acid concentrations that did not reach statistical significance after CLP were further aggravated in the indomethacin-treated rats.

The amount of indomethacin used in the present study and the time interval between different administrations were similar to those documented previously to block effectively the increased prostaglandin synthesis during endotoxin shock.[22,24,25] Thus, the lack of effect of indomethacin in our first two experiments was probably not due to ineffective tissue concentrations of the substance. However, to explore that possibility further, a third experiment was performed in which indomethacin was added *in vitro* to incubated muscles at a concentration known to reduce prostaglandin synthesis.[4] In this experiment also, indomethacin did not affect proteolytic rate in septic muscles, nor did it reduce the accelerated protein degradation caused by septic plasma, despite the fact that PGE_2 release by the muscles was reduced by about 50%.

The results of the third experiment also showed that indomethacin did not affect protein breakdown in normal muscle. Similar results were reported previously by Rodeman and Goldberg[4] and by Clark et al.[26] Thus, there seems to be agreement that prostaglandins do not regulate protein degradation in skeletal muscle under normal conditions. The results of the present study also suggest that increased prostaglandin levels alone are not responsible for accelerated muscle proteolysis during sepsis.

The present results are in line with a paper published while this study was in progress.[26] In that report, protein degradation in incubated epitrochlearis muscle from rats was increased by about 60% following burn injury. Administration of indomethacin (3 mg/kg/8 h starting 2 hours before burn) did not affect the elevated protein breakdown despite the fact that PGE_2 release by the incubated muscles was reduced from 22.1 to 8.5 ng/g/2 h. Also, when indomethacin was added *in vitro* (3 μM) to incubated muscles from burned rats, PGE_2 release by the muscles decreased, but the high rate of protein degradation was not reduced.[26]

Trauma and sepsis are usually accompanied by fever, at least initially, and a role of increased body temperature *per se* for enhanced muscle proteolysis was suggested recently.[27] The present results demonstrate that fever is not a prerequisite for accelerated protein breakdown during sepsis, since body temperature was decreased in our septic animals. One effect of indomethacin is to reduce body temperature by blocking PGE_2 release in the hypothalamus.[5,7] In contrast, body temperature was increased by indomethacin treatment of septic rats in the present study. This effect on body temperature might reflect a better preserved tissue perfusion, since the hemoconcentration observed during early sepsis was not present in the indomethacin-treated rats. In a previous report, indomethacin improved the hemodynamic status during endotoxin shock in dogs.[22]

Blood glucose was significantly reduced by indomethacin during early sepsis. Whether this result was due to a direct effect of indomethacin or indicates a role of prostaglandins for carbohydrate metabolism in sepsis cannot be answered by this study.

The finding that indomethacin did not improve survival following CLP is in contrast to several previous reports

in which this drug increased survival rates in different endotoxin and septic models.[22,23,25,28] The reason for this difference might be that CLP is an eventually fatal septic model. Survival rate or time was not improved by indomethacin in baboons given an LD_{100} dose of endotoxin.[24]

In conclusion, the present study does not support a role for prostaglandins in enhanced muscle proteolysis during sepsis. Since neither survival rate nor protein breakdown was affected by indomethacin, the suggestion to use this substance in the treatment of septic patients is open to question.

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