Effects of isoproterenol on myocardial structure and function in septic rats

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Effects of isoproterenol on myocardial structure and function in septic rats. J. Appl. Physiol. 86(3): 993–1001, 1999.—In
this study we sought to determine the effect of sepsis on two sequelae of prolonged (24-h) β-agonist administration, myocardial
hypertrophy and catecholamine-induced cardiotoxicity. Sprague-Dawley rats were randomized to cecal ligation and perforation (CLP) or sham study groups and then further randomized to receive isoproterenol (2.4 mg·kg
−2·day ·1 iv) or placebo treatment. At 24 h, myocardial function was
assessed by using the Langendorff isolated-heart technique or the heart processed for plain light microscopy. We found that 1) sepsis reduced contractile function, indicated by a rightward shift in the Starling curve (ANOVA with repeated
measures, sepsis effect, P < 0.002); 2) sepsis-induced myocardial
depression was reversed by isoproterenol treatment (isoproterenol effect, P < 0.0001); 3) sepsis reduced, but did not block, isoproterenol-induced myocardial hypertrophy (isoproterenol effect, P < 0.0001); 4) sepsis did not protect the
heart from catecholamine-induced tissue injury; 5) the septic heart
was protected against the effects of ischemia-reperfusion (decreased postreperfusion resting tension, ANOVA with repeated measures, P < 0.01), an effect attenuated by isoproterenol treatment (P < 0.005); and 6) sepsis reduced the incidence of sustained asystole or ventricular fibrillation after ischemia-reperfusion (P < 0.05), an effect also attenuated by isoproterenol treatment (P < 0.01). We conclude that, in sepsis, β-agonists induce changes in myocardial weight and function consistent with acute myocardial hypertrophy. These changes occur at the expense of significant tissue injury and increased sensitivity to ischemia-reperfusion-induced tissue injury.

infection; heart; circulation; peritonitis; ischemia-reperfusion

SHOCK IS THE EXTREME presentation of circulatory dys-
function complicating the sepsis syndrome and a com-
mon cause of mortality in the critically ill (3). Although
the cause of septic shock is likely multifactorial, a
depression in myocardial contractility is regarded as a
significant precursor of the circulatory compromise in
these patients (25). Because shock-induced tissue hy-
poperfusion may cause visceral injury in addition to
that caused by sepsis, β-agonists are commonly pre-
scribed to augment cardiac output and thereby main-
tain tissue perfusion pressure and oxygen delivery.
When administered for prolonged periods (>24 h) in
nonseptic conditions, high-dose β-agonists may result in
catecholamine-induced cardiotoxicity (29) and myo-
cardial hypertrophy (7, 20, 31). These data support the
hypothesis that similar changes may be seen in sepsis.
However, despite the potential clinical relevance of
such a finding, we were unable to identify experimental
studies in which this hypothesis had been tested.

Dose-dependent cardiotoxicity is the most important
adverse effect of prolonged (24-h) β-agonist adminis-
tration in animals (29), resulting in histological changes
that include myocyte necrosis, myofibrillar degenera-
tion, and leukocytic infiltration (29). Although more
difficult to study in human subjects, case reports sup-
port the view that similar pathological lesions are seen
in clinical situations where patients are exposed to
high-dose endogenous or exogenous catecholamines, as
occurs in severe asthma (24), phaeochromocytoma, and
severe head injury (28). A number of mechanisms have
been proposed to explain the pathogenesis of myocar-
dial injury caused by catecholamine exposure (16). One
hypothesis is that catechol-induced cardiotoxicity is
oxidant induced, resulting from free radicals derived
from catecholamine autoxidation (40) or ischemia-
reperfusion induced by coronary vasoconstriction (12).
Re-
levant to our understanding of this process in sepsis
are recent studies that demonstrate that inflammatory
stimuli may lead to the upregulation of myocardial
antioxidant activity (32, 41). These data suggest that,
in the context of sepsis, the heart may be significantly
protected from β-agonist-induced oxidant stress.
De-
spite the widespread use of catecholamines in septic
patients, the possible cardiotoxic effects of prolonged
catecholamine exposure have not been confirmed in
experimental studies.

Prolonged catecholamine exposure causes myocardial
hypertrophy in animals (7, 31), even in subhyper-
tensive doses (20). If data from other animal studies
(7, 15, 42) can be extrapolated to the septic state, β-agonist-
induced myocardial hypertrophy may represent an
adaptive response, partially reversing sepsis-induced
contractile dysfunction. Although we consider this a
plausible hypothesis, confirmatory experimental stud-
ies have not been reported in the literature. This is a
question of more than passing interest because the
physiological changes associated with sepsis [which
include inhibition of cardiac protein synthesis (2, 33)
and reduced myocardial sensitivity to β-adrenergic
stimulation in some animal models of sepsis (5)] may
prevent catecholamine-induced myocardial hypertro-
phy and thus prevent a physiologically relevant aug-
mentation in myocardial function when these agents
are used to treat septic shock.

With this background, we designed the present exper-
diment to determine the effects of high-dose β-agonist
administration on myocardial hypertrophy and catechol-
amine-induced cardiotoxicity. By using rats rendered septic by cecal ligation and perforation (CLP), our experimental objectives were threefold, namely, to determine whether a 24-h infusion of isoproterenol would 1) reverse the depression in myocardial contractility observed in sepsis (25, 39), 2) induce myocardial hypertrophy, and 3) cause tissue injury (29). We used the β<sub>1</sub>/β<sub>2</sub>-agonist isoproterenol to determine the myocardial consequences of long-term exposure to catecholamines for two reasons. First, α-agonists may independently cause myocardial protection (10). Second, the effect of isoproterenol on the heart has been extensively investigated in rats, in which, over a 24-h period, it causes dose-dependent myocardial injury (29) and myocardial hypertrophy (7, 31). In this experiment, sepsis attenuated, but did not prevent, the changes in myocardial weight (7, 31) and contractile function (15, 42) associated with myocardial hypertrophy after catecholamine exposure. And, although the septic myocardium did exhibit resistance to ischemia-reperfusion-induced injury [postreperfusion left ventricular developed pressure (LVDP) and percentage of animals with sustained ventricular fibrillation or asystole], in both control and septic by cecal ligation and perforation (CLP), our investigative approach allowed calculation of wet weight-to-dry weight ratios. In both protocols, hearts were processed for plain light microscopy without Langendorff perfusion (26). Before fixation, the heart was weighed so that the heart weight-to-body weight ratio could be calculated, and the remaining organs were harvested to allow calculation of wet weight-to-dry weight ratios. In both groups, animals were studied after a 24-h exposure to isoproterenol.

After anesthesia with halothane, internal carotid (PE 50, Intramedic) and external jugular lines (0.25-mm Silastic tubing, Dow Corning, Midland, MI) were inserted under sterile conditions. The lines were tunneled subcutaneously to the back of the neck, where they were attached to a swivel device. Animals were then randomized to either sham or CLP groups and then further randomized to receive isoproterenol (2.4 mg·kg<sup>−1</sup>·day<sup>−1</sup>) or placebo treatment (normal saline) as an infusion over 24 h. Sham animals had insertion of lines only. In the CLP group, a ligature was placed around the cecum immediately distal to the ileocecal valve. The cecum was then punctured twice with an 18-G needle. After the animals recovered from anesthesia, the following infusions were commenced in both groups: normal saline at 300–400 ml·kg<sup>−1</sup>·day<sup>−1</sup>, heparin at 400 U·kg<sup>−1</sup>·day<sup>−1</sup>, and fentanyl at 400 µg·kg<sup>−1</sup>·day<sup>−1</sup>. Heparin was administered to ensure patency of intravascular lines, and fentanyl provided postoperative analgesia. Water and laboratory chow were available ad libitum. The study protocol was reviewed and approved by the University of Western Ontario Committee on Animal Care.

Assessment of myocardial function. Twenty-four hours after randomization, animals were lightly anesthetized with phenobarbital (30 mg/kg ip), and, after decapitation, the heart was rapidly excised and perfused on a Langendorff apparatus at 37°C with Krebs-Henseleit solution of the following composition (in mM): 120 NaCl, 4.8 KCl, 1.2 KH<sub>2</sub>PO<sub>4</sub>, 1.2 MgSO<sub>4</sub>, 1.25 CaCl<sub>2</sub>, 25 NaHCO<sub>3</sub>, and 11 glucose. The perfusion buffer was equilibrated with a 95% O<sub>2</sub>-5% CO<sub>2</sub> gas mixture. LVDP and its first derivative (LV/dP<sub>t</sub>) were monitored by using a latex balloon (compliant volume > 130 µl) secured in the left ventricular cavity. Coronary perfusion pressure (CPP), which reflects coronary vascular resistance under constant-flow conditions, was monitored through the Langendorff column by means of a fluid-filled catheter connected to a pressure transducer (Inflow, Baxter, Toronto, ON). Data were recorded on a chart recorder (Gould 8188 recorder and modules 13–4615–50 and 13–4615–71). After a 35-min equilibration period, the heart was paced at 360 beats/min by using a Grass stimulator (SD5) and ventricular pacing wires. We measured baseline myocardial function at a preload of 5 mmHg and a coronary flow rate of 10 ml/min. Recorded parameters included LVDP, LV dP/dt, +dP/dt<sub>max</sub>, and CPP, where dP/dt is the first derivative of LVDP. The differential ratio was calculated by dividing +dP/dt<sub>max</sub> by dP/dt<sub>max</sub> (14). Two additional measurements of contractile function were recorded: 1) a Starling curve over a range of preloads of −5 to 20 mmHg at a coronary flow rate of 10 ml/min and 2) a ventricular performance-coronary flow rela-

![Fig. 1. Experimental design. Sham, sham-operated animals; CLP, cecal ligation and perforation.](http://jap.physiology.org/10.12022460.png)
RESULTS

Model. No mortality was seen in the CLP- or sham-treated groups. The mortality in the isoproterenol and isoproterenol + CLP-treated animals was 20 and 35%, respectively (logistic regression, isoproterenol effect, P < 0.01; sepsis effect, P < 0.05). Table 1 lists physiological data from animals in whom morphometry and in vitro myocardial function were studied. Twenty-four hours after CLP, a mild reduction in blood pressure attributable to both sepsis and isoproterenol treatment was recorded. Hematologic changes consistent with sepsis, such as a reduction in the leukocyte and platelet count, were also noted at this time. Generalized peritonitis was confirmed at postmortem in all CLP animals.

Myocardial function before ischemia-reperfusion. Sepsis was associated with a reduction in LVDP and −dP/dt max and a significant increase in both coronary vascular resistance and the differential ratio (Table 2). Treatment with isoproterenol increased LVDP, +dP/dt max, and −dP/dt max and decreased coronary vascular resistance and the differential ratio. When the effect of preload on myocardial function in the four study groups is analyzed, analysis of variance showed that LVDP was significantly reduced by CLP treatment and augmented by isoproterenol treatment over a range of preloads from −5 to 20 mmHg (Fig. 1A). Comparisons between isoproterenol-treated and untreated groups, at each level of preload, showed that isoproterenol treatment augmented contractility in both CLP- and sham-treated groups (Fig. 1A). Figure 2B shows there was no difference in the myocardial intraventricular pressure vs. EDV curves (i.e., compliance) among the four experimental groups during this baseline examination. Over a range of flows from 2.2 to 13 ml/min, analysis of variance showed that the contractile response to increased coronary flow was depressed by

Table 1. Physiological data collected from rats after 24 h of sepsis

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>CLP</th>
<th>CLP + Isoproterenol</th>
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<tbody>
<tr>
<td>Time, h</td>
<td>24 h</td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>MABP, mmHg</td>
<td>120 ± 3</td>
<td>98.8 ± 3.3*</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.45 ± 0.01</td>
<td>7.4 ± 0.01*</td>
<td></td>
</tr>
<tr>
<td>Paco2, Torr</td>
<td>39.0 ± 1.2</td>
<td>41.2 ± 1.6</td>
<td></td>
</tr>
<tr>
<td>Paco2, Torr</td>
<td>70 ± 5.1</td>
<td>78.7 ± 4.4</td>
<td></td>
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<tr>
<td>WCC, ×10⁹/l</td>
<td>9.8 ± 0.6</td>
<td>3.7 ± 0.2*</td>
<td></td>
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<tr>
<td>Hb, g/l</td>
<td>133.5 ± 1.8</td>
<td>126.5 ± 4.4</td>
<td></td>
</tr>
<tr>
<td>Platelet count, ×10⁹/l</td>
<td>813 ± 34</td>
<td>558 ± 40*</td>
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<tr>
<td></td>
<td>Sham + Isoproterenol</td>
<td>CLP + Isoproterenol</td>
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<tr>
<td>Time, h</td>
<td>24 h</td>
<td>24 h</td>
<td></td>
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<tr>
<td>n</td>
<td>19</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>MABP, mmHg</td>
<td>100 ± 3t</td>
<td>88.8 ± 2.9*†</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.43 ± 0.01</td>
<td>7.43 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Paco2, Torr</td>
<td>37.6 ± 1.0</td>
<td>33.2 ± 1.2*†</td>
<td></td>
</tr>
<tr>
<td>Paco2, Torr</td>
<td>71.3 ± 4.1</td>
<td>84.6 ± 5.0</td>
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</tr>
<tr>
<td>WCC, ×10⁹/l</td>
<td>9.0 ± 0.6</td>
<td>5.7 ± 0.4*</td>
<td></td>
</tr>
<tr>
<td>Hb, g/l</td>
<td>108.1 ± 2.4t</td>
<td>110.3 ± 3.2t</td>
<td></td>
</tr>
<tr>
<td>Platelet count, ×10⁹/l</td>
<td>733 ± 21</td>
<td>522 ± 32†</td>
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</table>

Values are means ± SE, n. No. of animals; Sham, sham-operated animals; CLP, cecal ligation and perforation; MABP, mean arterial blood pressure; Paco2 and Paco2, arterial Pco2 and Paco2, respectively; WCC, white cell count. Data were collected immediately before harvesting the heart for histology or in vitro functional assessment. Values were compared by using an unpaired t-test. Sepsis effect, *P < 0.05; isoproterenol effect, †P < 0.05.
resting tension primarily in sham-treated animals (Fig. 6B). The proportion of hearts that did not recover contractile function (asytoste or ventricular fibrillation) after 60 min of reperfusion was highest in the sham isoproterenol-treated group (Fig. 7).

**DISCUSSION**

When administered in high doses to normal animals for 24 h, β-agonists cause myocardial hypertrophy (7, 31) and cardiotoxicity (29). In rats made septic by CLP, CLP treatment and augmented by isoproterenol treatment (Fig. 3A). Comparisons between isoproterenol-treated and untreated groups, at each level of coronary flow, showed that isoproterenol treatment augmented contractility in both sham- and CLP-treated animals. In the CLP group, reductions in coronary flow were accompanied by an increase in left ventricular EDV (Fig. 3B). Analysis of variance showed that, over the range of flows studied, isoproterenol reduced coronary resistance and sepsis increased coronary resistance (Fig. 3C). Although an increase in the ratio of the heart wet weight to body weight was seen after treatment with isoproterenol in both treatment groups, this finding was less marked in the CLP group (Fig. 4A). No difference in the mean body weight was seen among the four experimental groups. Tissue injury scores demonstrated that, at the dose used in this study, isoproterenol caused significant myocardial injury. The extent of this injury was unaffected by CLP treatment (Fig. 4B). Analysis predicts that it would have been possible to detect a difference in the tissue injury score of 0.95 with a power of 80% (comparison of the isoproterenol-treated groups by using a unpaired two-tailed t-test). Wet weight to dry weight ratios, performed in other viscera, showed that CLP caused a significant increase in tissue water content in selected intra-abdominal organs (Fig. 5). The extent of these changes was not altered by isoproterenol.

Myocardial function after ischemia-reperfusion. After 30 min of ischemia followed by reperfusion, LVDP recovered more completely in CLP animals compared with sham-treated control animals (Fig. 6A). Analysis of variance showed that, after reperfusion, left ventricular resting tension was decreased in CLP-treated animals and elevated in isoproterenol-treated animals (Fig. 6B). Comparisons between isoproterenol-treated and untreated groups at each measured time point showed that isoproterenol increased postreperfusion

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**Table 2. In vitro cardiac performance at baseline**

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>CLP</th>
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<tbody>
<tr>
<td><strong>n</strong></td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td><strong>LVDP, mmHg</strong></td>
<td>68.1 ± 6.4</td>
<td>48.1 ± 5.0*</td>
</tr>
<tr>
<td>+dP/dt_max, mmHg/s</td>
<td>4572 ± 424</td>
<td>3484 ± 362</td>
</tr>
<tr>
<td>−dP/dt_max, mmHg/s</td>
<td>3062 ± 269</td>
<td>2070 ± 256*</td>
</tr>
<tr>
<td><strong>Differential ratio</strong></td>
<td>1.48 ± 0.05</td>
<td>1.71 ± 0.07*</td>
</tr>
<tr>
<td><strong>CPP, mmHg</strong></td>
<td>60.2 ± 4.8</td>
<td>81.8 ± 8.3*</td>
</tr>
<tr>
<td><strong>CVR, mmHg·ml⁻¹·h⁻¹</strong></td>
<td>0.10 ± 0.02</td>
<td>0.14 ± 0.05*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, No. of animals; LVDP, left ventricular developed pressure; dP/dt_max, maximal first derivative of LVDP; CPP, coronary perfusion pressure; CVR, coronary vascular resistance. Data were collected at a preload of 5 mmHg and coronary flow of 10 ml/min. Values were compared by using analysis of variance. Sepsis effect, *P < 0.05; isoproterenol effect, †P < 0.05.
we found that sepsis did not prevent the increase in myocardial weight (7, 31) and contractility (15, 42) associated with catecholamine-induced acute myocardial hypertrophy. Furthermore, although sepsis protected the heart against ischemia-reperfusion-induced injury (postreperfusion LVDP and percentage of animals with sustained ventricular fibrillation or asystole), it did not protect the heart from catecholamine-induced injury, assessed by using plain light microscopy. These data suggest that catecholamine-induced acute myocardial hypertrophy and myocardial injury are pathophysiological mechanisms of potential relevance when high-dose β-agonists are administered in the context of sepsis-induced myocardial dysfunction.

Experimental model and design. Focal bacterial infection is a common cause of infection in critically ill patients. The rat CLP model mimics many of the features of this clinical condition (23) and is therefore widely used to study the sepsis syndrome. In our fluid-resuscitated model of sepsis (23), blood pressure, cardiac output, and coronary blood flow are all well maintained, thus providing experimental conditions suitable to study normotensive sepsis. To determine the effects of isoproterenol infusion on myocardial structure and function in sepsis, we designed a 24-h infusion model because 1) catecholamines are usually administered for such protracted periods in patients with sepsis and 2) experimental models have shown that this duration of isoproterenol administration (at the dose used in this study) causes readily quantifiable myocardial hypertrophy and catecholamine-induced tissue injury (7, 31), end points that were relevant to the hypotheses tested in the present study. Although the dose used in this study (2.4 mg·kg\(^{-1}\)·day\(^{-1}\)) is greater than the maximum recommended dose for this agent in humans (0.6 mg·kg\(^{-1}\)·day\(^{-1}\)), it was selected because the physiological effects of this dose of isoproterenol have been well characterized in rats (7, 31). Because a number of physiological stimuli, such as ischemia, thermal stress, and cytokine exposure, protect the heart against oxidative injury [i.e., delayed preconditioning (32, 41)], we also incorporated measurements of myocardial recovery after ischemia-reperfusion into the present experiment.

Fig. 3. Effect of coronary flow on developed pressure, change in EDV, and coronary resistance. A: relationship between coronary flow and developed pressure. Sepsis effect, P < 0.05; Iso effect, P < 0.001 (ANOVA with repeated measures). Comparisons between ISO-treated and untreated groups showed that ISO treatment augmented contractility in both CLP- and sham-treated groups (comparison of least squares means: *P < 0.05, CLP vs. CLP-Iso treatment; △P < 0.05, sham vs. sham-Iso treatment). B: relationship between EDV and coronary flow at a preload of 5 mmHg. EDV is expressed as change in EDV compared with baseline measured at a coronary flow of 10 ml/min. Sepsis effect, P < 0.05 (ANOVA with repeated measures). Comparison between sham and CLP groups at each level of flow: *P < 0.05 (comparison of least squares means). C: relationship between coronary resistance and coronary flow. Sepsis effect, P < 0.05 (ANOVA with repeated measures). Comparison between sham and CLP groups at each level of flow: *P < 0.05 (comparison of least squares means).
Effect of sepsis and isoproterenol on myocardial weight and function. Sepsis is associated with both systolic and diastolic dysfunction. Consistent with data from previous human (25) and animal studies (39), we found that measurements of myocardial systolic function were depressed 24 h after CLP. We also noted that CLP was accompanied by an increase in the differential ratio (the ratio of $\frac{1}{2}\frac{dP}{dt}$ to $\frac{2}{3}\frac{dP}{dt}$), which is consistent with a proportionally more severe effect of sepsis on diastolic relaxation. In contrast, isoproterenol infusion during the development of sepsis completely prevented the reduction in systolic and diastolic function seen in the CLP-treated group (Figs. 2 and 3, Table 2). Although previous studies suggested that chronic catecholamine administration may improve adrenergic signaling (27), the majority of studies in this area show that the chronic administration of $\beta$-agonists leads to downregulation of adrenergic signaling (36) and myocardial hypertrophy (7, 20, 31). These data suggest that the isoproterenol-induced augmentation in myocardial systolic and diastolic function seen in the present study may have been due to myocardial hypertrophy. Consistent with this view, we noted the isoproterenol administration in septic animals was associated with an increase in the heart weight-to-body weight ratio, thereby suggesting that such functional effects may have resulted from catecholamine-induced acute myocardial hypertrophy. This novel observation in septic animals is consistent with data from other animal studies, which show that catecholamine-induced acute myocardial hypertrophy is accompanied by improved myocardial systolic and diastolic function (15, 42). In addition, our data suggest that the degree of isoproterenol-induced hypertrophy (assessed by the heart weight-to-body weight ratio) was less in CLP-treated compared with sham-treated animals (Fig. 4A). However, this lesser increase in myocardial mass in the CLP group was associated with a trend toward a proportionally greater isoproterenol-induced augmentation of myocardial contractile function in the septic group (Fig. 2). This finding suggests an altered relationship between the structural and functional correlates of isoproterenol-induced myocardial hypertrophy in sepsis. A possible explanation for this observation is an effect of sepsis on the pattern of expression of functionally important hypertrophy-related genes, such as the various isoforms of the myosin heavy chain (7).

Previous studies have shown that CLP is associated with an increase in plasma epinephrine and norepinephrine levels (18). The physiological concentrations of these $\beta$-agonists is, however, an order of magnitude less than the pharmacological doses of catecholamines.
used in the treatment of septic shock (11, 18). Because we did not observe functional (Fig. 2B) or structural evidence of hypertrophy in our CLP-treated animals (Fig. 4A), it is unlikely that sepsis-induced changes in plasma catecholamine levels (18) result in myocardial hypertrophy of physiological relevance.

Effect of sepsis and isoproterenol on tissue morphometry. Some animal studies have shown that sepsis causes histological evidence of tissue injury (reviewed in Ref. 26). In a previous study using this model, however, we were unable to demonstrate an association between sepsis and changes in myocardial vascular permeability or ultrastructure (assessed by electron microscopy) (26). Using plain light microscopy, the present study confirmed this previous observation. We also found that isoproterenol, at the doses used in the present study, caused myocardial necrosis (Fig. 4B), an expected observation on the basis of the work of Rona and co-workers (29).

Previous studies have shown that a number of treatments may protect the heart against isoproterenol-induced tissue injury, including prior exposure to low-dose isoproterenol (9) and prior ischemia-reperfusion (30). In the present study, we found that sepsis did not protect against isoproterenol-induced tissue injury. A possible explanation for this observation may be that isoproterenol-induced injury occurred before the induction of sepsis-induced delayed preconditioning, a process that evolves over a period of 24 h (41). If this is the case, it is possible that a protective effect may be seen if the initiation of isoproterenol exposure had been delayed for a 24-h period. Therefore, the present study does not exclude the possibility that sepsis may protect against isoproterenol-induced tissue injury.

However, our findings have a number of practical implications. First, because catecholamines are commonly used in parallel with the development of severe sepsis, our data suggest that sepsis-induced upregulation of myocardial antioxidant defenses (see Fig. 6 and Ref. 32) would not protect against catecholamine-induced myocardial toxicity in clinical practice. Second, we found that the functional effects of isoproterenol-induced myocardial injury were masked by the induction of myocardial hypertrophy. Therefore, if β-agonist-induced cardiotoxicity is seen in the clinical context, it may only be of functional significance at a very late stage. This may explain the low incidence of reports of catecholamine-induced tissue injury in the clinical literature.

Effect of sepsis and isoproterenol on functional recovery after ischemia-reperfusion. The myocardium is protected from the injurious effects of ischemia-
rerefusion by preexposure to a number of stimuli such as heat, ischemia, and the administration of cytokines (32, 41). Although this protection wanes after 60–120 min (41), a second window of protection is seen 24 h later and has been termed “delayed preconditioning” (41). This latter phenomenon accounts for the increased resistance of the septic myocardium to ischemia-reperfusion after the administration of endotoxin, endotoxin-like compounds, tumor necrosis factor, and interleukin-1 (41). The physiological basis of delayed preconditioning is believed to be upregulation of endogenous antioxidants that may be induced by heat stress, cytokine exposure, endotoxin administration, and ischemia (32, 41). End points that are measured to confirm delayed preconditioning include improved postischemic contractile function (41) and protection against arrhythmias (38).

Only a few studies have examined delayed myocardial protection in models of focal bacterial sepsis. McDonough and Causey (22) reported that sepsis improved contractile recovery after ischemia-reperfusion in rats made septic by the subcutaneous injection of Escherichia coli. In a previous study using the CLP model, we reported that sepsis caused a reduction in resting tension after ischemia-reperfusion (26). Such data are consistent with the concept that sepsis induces myocardial protection, because previous studies have demonstrated that ischemic contracture correlates with the time course of myocardial high-energy phosphate depletion and myocardial injury (17). In the present study, as well as demonstrating an effect of sepsis on post-ischemia-reperfusion resting tension, we confirmed that sepsis improved contractile function postreperfusion (Fig. 6A) and decreased the frequency of postreperfusion arrhythmias (Fig. 7). Beckman and colleagues (4) found that doses of norepinephrine, sufficient to cause myocardial hypertrophy, increased survival in dogs after embolization of the coronary circulation with microspheres. In that study, the majority of the deaths were due to ventricular fibrillation within 15 min of coronary embolization. These findings differ from the results of the present study, where we found that high-dose isoproterenol, in a dose sufficient to cause myocardial hypertrophy, increased the susceptibility of the heart to ischemia-reperfusion (Fig. 3) both in sham and, to a lesser extent, in septic animals (Fig. 3B). Although not consistent with the work of Beckman et al., our data are similar to prior studies that have shown that the hypertrophied ventricle is more susceptible to the effects of ischemia-reperfusion (1). In addition, data suggesting that α-agonists may cause myocardial protection against ischemia-reperfusion (10) provide a possible explanation for the disparate results in the study by Beckman et al., where myocardial hypertrophy was induced by a mixed α- and β-agonist (norepinephrine) rather than by a pure β-agonist (isoproterenol) alone.

Summary. No previous studies have determined the effect of sepsis on two important sequelae of β-agonists when administered in high doses over a period of 24 h: acute myocardial hypertrophy (31, 7) and catecholamine-induced cardiotoxicity (29). Such a preclinical study is relevant to our understanding of the potential effects of β-agonists when they are used in high doses in human sepsis. We found that sepsis did not prevent changes in myocardial weight and contractile function consistent with isoproterenol-induced acute myocardial hypertrophy. Furthermore, although the septic myocardium did exhibit resistance to ischemia-reperfusion-induced injury (postreperfusion LVDP and percentage of animals with sustained ventricular fibrillation or asystole), in both control and isoproterenol-treated animals, there was no simultaneous protection against isoproterenol-induced myocardial injury. These data suggest that catecholamine-induced myocardial hypertrophy and myocardial injury are pathophysiological mechanisms of potential relevance when high-dose β-agonists are administered to treat sepsis-induced myocardial dysfunction.

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