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Cardiac Function and Coronary Flow in Chronic Endotoxemic Pigs (42805)

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Abstract. We have reported that myocardial inotropism was depressed in acute and chronic endotoxemia. One possible mechanism for this observation is that endotoxemia reduces myocardial perfusion and indeed, we observed reduced myocardial perfusion in acute endotoxemia. This study tested the hypothesis that reduced inotropism of chronic endotoxemia was accompanied by reduced coronary artery blood flow. Fifteen pigs were equipped with left atrial and ventricular catheters, circumflex coronary and pulmonary artery flow meters, left ventricular pressure transducer, and ultrasonic crystals in the anterior–posterior axis to measure internal short axis diameter by sonomicrometry. The pigs recuperated for 3 days before basal data were collected over the next 3–5 days. After at least 7 postoperative days, an osmotic pump containing *Salmonella enteriditis* endotoxin was implanted in 12 pigs. Endotoxin was delivered at 10 μg/hr/kg for 2 days, at which time the animals were sacrificed. Osmotic pumps containing sterile saline were implanted in 3 pigs. Eight of the 12 endotoxemic pigs survived; 4 died before the morning of the second day. The survivors exhibited elevated heart rate, peak left ventricular systolic pressure, and cardiac output. Inotropism was evaluated by calculating the slope of the end-systolic pressure–diameter relationship (ESPDR) and % diameter-shortening. ESPDR was significantly depressed on the second endotoxemic day, while % diameter-shortening was depressed on both endotoxemic days. Coronary artery blood flow was significantly elevated on both endotoxemic days, while cross-sectional stroke work was unchanged. Therefore, the ratio of coronary blood flow to stroke work increased on both endotoxemic days. Nonsurvivors exhibited reduced heart rate, cardiac output, peak left ventricular systolic pressure, ESPDR, and % diameter-shortening. Neither coronary artery blood flow nor flow-to-work ratios increased in this group. Sham endotoxemic pigs demonstrated no cardiac or hemodynamic changes over 3 days. These results indicate that depressed inotropism during chronic endotoxemia was not caused by reduced coronary blood flow; rather, the myocardium was relatively overperfused.
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Previous studies have shown that myocardial inotropism is depressed in acute shock states induced by acute endotoxemia (1, 2), splanchnic artery occlusion (4), acute pancreatitis (5), and during chronic intravenous infusion of low doses of endotoxin (3). However, the mechanisms which mediate reduced inotropism have not been fully elucidated. Direct depression of the myocardium by endotoxin appears to be unlikely because Parker and Adams (6) have shown that endotoxin added to the perfusate of isolated hearts did not reduce contractile function. We infused endotoxin directly into the coronary circulation of intact pigs and saw no regional contractile or electrical abnormalities. Our previous study of acute endotoxemia (1) showed reduced intropism coincident with reduced myocardial perfusion. It is well known that reduced blood flow to the myocardium will impair contractile function (7). This study tested the hypothesis that reduced inotropism observed in chronic endotoxemia was caused by reduced coronary blood flow.

This hypothesis was tested in 15 pigs by measuring pulmonary and coronary artery blood flow, left ventricular pressure, and internal short-axis diameter. Inotropic state before and during chronic endotoxemia was assessed by calculating the slope of the end-systolic pressure–diameter relationship and % diameter-shortening. The model of chronic endotoxemia employed closely resembles clinical systemic sepsis because of its long time duration (>3 days) and its low administered endotoxin dose (10 μg/kg/hr). Indeed, many of the cardio- and hemodynamic perturbations of chronic endotoxemia replicate clinical findings.

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Materials and Methods. Fifteen Yorkshire pigs weighing between 25 and 30 kg were premedicated with ketamine HCl (15 mg/kg) and sodium thiopental (10 mg/kg). The animals were intubated and ventilated by a Harvard respirator. Surgical anesthesia was maintained using enflurane (3–5% induction, 1–3% maintenance) and nitrous oxide (30%) in oxygen. A left thoracotomy was performed using sterile techniques in an AAALAC approved, large animal surgical suite. Postoperative antibiotic treatment was 400,000 IU of penicillin onto the incision, and 400,000 IU of penicillin im. No postoperative or postmortem sign of infection was observed.

Cardiac instrumentation. A left thoracotomy was performed at the fifth intercostal space, the heart was exposed, the pericardium was opened, and was sutured to the chest wall to form a cradle. Two 5 mm hemispherical, ultrasonic, pizoelectric crystals (Channel Industries, Santa Barbara, CA) were implanted on the endocardial surfaces of the anterior and the posterior walls of the left ventricle approximately one-third of the distance between base and apex. An oscilloscope was used to ensure proper alignment of the crystals. These crystals were used to measure internal short-axis diameter (D) by pulse-transit sonomicrometry (Triton Technology, San Diego, CA). The intramyocardial electrocardiogram (ECG) was recorded from these crystals.

Left ventricular pressure (P) was measured by a micromanometer on the tip of a catheter (Kongisberg Instruments, Pasadena, CA) implanted within the left ventricle through the apex and verified by measuring pressure through a catheter filled with saline placed within the ventricle. A second fluid-filled catheter was placed in the left atrium and was used to infuse drugs.

Cardiac output and coronary artery flow were measured by ultrasonic flow meters (Transonic Systems, Inc., Ithaca, NY) implanted around the pulmonary and left circumflex coronary arteries. In pigs, there is insufficient space between the aortic root and the carotid arteries to implant a flow meter, so flow through the pulmonary artery was measured and considered as cardiac output. The ultrasonic flow meters were calibrated by the factory in units of liters per minute or milliliters per minute; these calibration values were confirmed postmortem.

Protocol. Pigs were equipped with instruments on Day 0 and were allowed to recuperate for 3 days before recording basal hemo- and cardiodynamic values. Basal recordings were obtained daily between Days 3 and 10 following surgery. Each animal was alert, moved freely, demanded food frequently, and had stable hemodynamic readings by the third postoperative day. After 7–10 days of basal recordings, an osmotic pump (Alzet Model 2 ML1, Palo Alto, CA) was implanted using sterile surgical techniques while the animals were under ketamine sedation and gaseous anesthesia. The pump contained *Salmonella enteriditis* endotoxin which was reconstituted in sterile saline. The osmotic pump delivered endotoxin continuously at 10 μg/kg/hr without the need for external connections or frequent handling of the animals. A midline incision was made in the pig's neck, the internal jugular vein was isolated, and ligatures were placed around this vein. The output tube of the osmotic pump was attached to 0.7 mm i.d. Teflon tubing (MER Chromatographic, No 302, Mountain View, CA). The Teflon tubing was inserted into the jugular vein and advanced until the entire length of the tube was inside the vessel. The Teflon tubing was cut to a length calculated to begin delivering endotoxin 16 ± 2 hr after the pump was implanted. Osmotic pumps filled with sterile saline were implanted in 3 pigs to be sham endotoxemia controls. In addition, each endotoxemic animal served as its own control, so changes from the basal state induced by endotoxin could be measured and compared statistically.

Cardiodynamic data acquisition and analysis. All recordings were made with a Gould-Brush 480 recorder whose analog output was fed into an IBM PC-AT through an analog-to-digital conversion board (Model 2801A, Data Translation, Marlborough, MA). A detailed description of the computerized data collection and analysis techniques employed have been previously reported (8). Left ventricular pressure (P), short axis diameter (D), pulmonary artery blood flow, coronary artery blood flow, and a trigger pulse from an

R-wave sensor were collected for 30 sec and digitized at 200 Hz. In cases where the electrocardiogram was abnormal (e.g., exaggerated T-wave), pressure triggering was used to define end-diastole (20 msec prior to LVP = 40 mm Hg). The 30-sec observation period was divided into sequential beats and data from each beat were examined separately. dP/dt, elastance (P/D), cross-sectional stroke work ($\pi\ [D/2]^2 dP$), and instantaneous and integrated flow values were calculated from the primary data. Selected data from each beat were stored in a two-dimensional beat profile (value of the variable vs time during the beat) and sequential beats were laminated in the time dimension to produce a three-dimensional beat matrix.

Observations were made during steady state, while the pig was resting quietly, and during the response to intraatrial injection of 1 μg of angiotensin. This dose progressively raised systolic pressure 15–25 mm Hg and provided a sufficiently wide range of end-systolic pressures and diameters to calculate the slope of end-systolic pressure–diameter relationship (ESPDR). It was calculated by first determining the values of P and D when P/D is maximal for each beat. These P and D values from 40–50 sequential beats define the line ESPDR; the slope and intercept of the ESPDR line was calculated using least-squares linear regression. Regression ANOVA determined the goodness of fit of these data; observations in which the r^2 value was less than 0.4 were discarded.

Statistical tests. Eight of the 12 endotoxemic pigs survived to the third day of chronic endotoxemia and 4 died before the second day of endotoxemia. Cardiodynamic and coronary flow data were obtained on each postsurgical day, Days 3–10 postsurgery. The data describing the basal condition of each animal were considered to be the 10 observation pairs (steady state and angiotensin infusion) made on the day before implantation of the osmotic pump. These data were statistically compared to 10 observational pairs on each endotoxemia day by two-way analysis of variance. Data from nonsurviving pigs were also analyzed by two-way ANOVA. All values are reported as means ± SEM, and statistical significance was determined at $P < 0.05$.

Results. Chronic endotoxin infusion (CET) into pigs produced either sustained increase in cardiac output, heart rate, and peak left ventricular systolic pressure which persisted for 2 days or profound decrease in cardiac output followed by expiration within 24 hr. Figures 1–4 show data from the surviving pigs; Table I shows the data from nonsurvivors. Chronic sterile saline infusion into 3 pigs did not alter any measured cardio- or hemodynamic parameters.

Figure 1 shows peak left ventricular systolic pressure, heart rate, and cardiac output in the surviving group. Peak LV systolic pressure was elevated from 109 ± 4.1 to 112 ± 4.8 (Day 1 CET) and to 116 ± 3 mm Hg (Day 2 CET, $P < 0.01$). Cardiac output and heart rate were significantly elevated on both endotoxemia days, increasing from 2.9 ± 0.5 to 3.3 ± 0.4 and 3.3 ± 0.5 liters/min on Days 1 and 2, respectively. Heart rate increased from 111 ± 5 to 133 ± 4 and 149 ± 5 bpm on Days 1 and 2, respectively. Because of the higher heart rates, stroke volume (not shown) fell from 21.6 ± 0.9 to 20.7 ± 1.5 and 18.4 ± 1.3 ml/beat on Days 1 and 2, respectively. All values were significantly different (two-way ANOVA).

Figure 2 shows the changes in left ventricular end-diastolic diameter, % diameter-shortening, and the slope of ESPDR. End-diastolic diameter, an accurate estimate of preload, rose slightly on the first day of endotoxemia and rose significantly on the second day (from 36.9 ± .8 to 37.5 ± .4 to 39.5 ± .6 mm), respectively. % Diameter-shortening, an estimate of ejection fraction, was significantly depressed on both days of endotoxemia, dropping from 15.1 ± 1.0 to 12.7 ± 0.9 and 11.9 ± 1.2% on Days 1 and 2, respectively. The slope of ESPDR was unchanged on the first day of endotoxemia, but became significantly depressed on the second day (13.9 ± 1.8 to 14.1 ± .8 to 11.3 ± 2.7 mm Hg/mm, $P < 0.01$ on Day 2 CET). In a previous study using this model, we observed declines in ESPDR on both CET days (3). Neither $+dP/dt_{max}$ or $-dP/dt_{max}$ (not shown) changed significantly.

Figure 3 shows coronary flow and cross-sectional stroke work per minute. Stroke work was calculated by integrating over the beat's duration the product of diameter

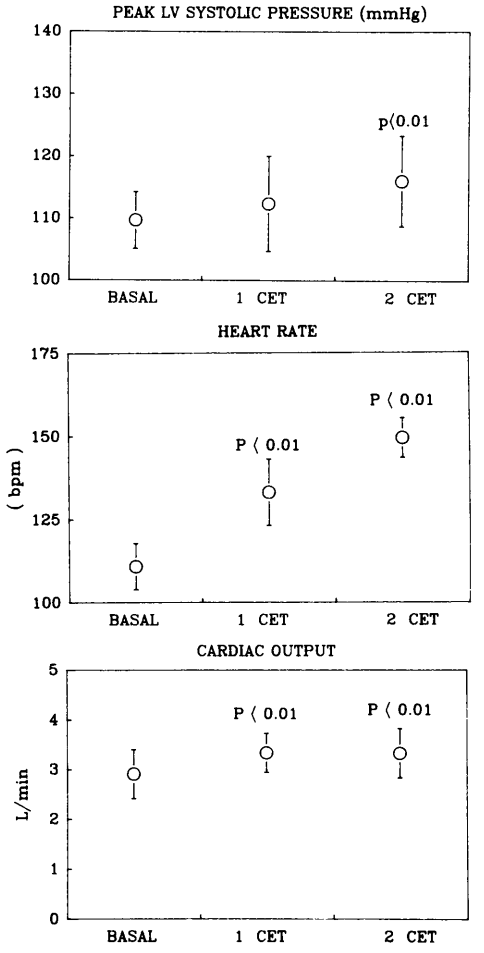

FIG. 1. Peak left ventricular systolic pressure, heart rate, and cardiac output during the basal state and Days 1 and 2 chronic endotoxemia (CET). Peak LV systolic pressure was significantly elevated on the first endotoxemic day, while heart rate and cardiac output were significantly elevated on both endotoxemic days. Eight pigs were studied. Each animal's data consisted of 10 basal observations immediately before endotoxemia and 10 observations on each endotoxemic day. Data were compared using two-way analysis of variance; $P < 0.01$ are indicated. Values are means ± 1 SEM.

cross-sectional area (π $[D/2]^2$) times pressure (dP). We determined that this value accurately estimated stroke volume (measured by the pulmonary flow meter). Cross-sectional stroke work per minute was significantly elevated only on the second endotoxemia day (rising from 699 ± 63 to 823 ± 103 cm^2 mm Hg). Coronary artery flow per minute increased from 16.9 ± 1 to 29.2 ± 1.7 to 29.5 ± 2 ml/min on Days 1 and 2 of endotoxemia, respectively.

Figure 4 shows coronary flow and cross-sectional stroke work per beat and the flow/work ratio. Coronary flow per beat increased significantly on both endotoxemia days, rising from 155 ± 29 to 225 ± 28 to 195 ± 27 μl/bt on endotoxemia Days 1 and 2, respectively. Stroke work per beat was unchanged during endotoxemia. However, the ratio of

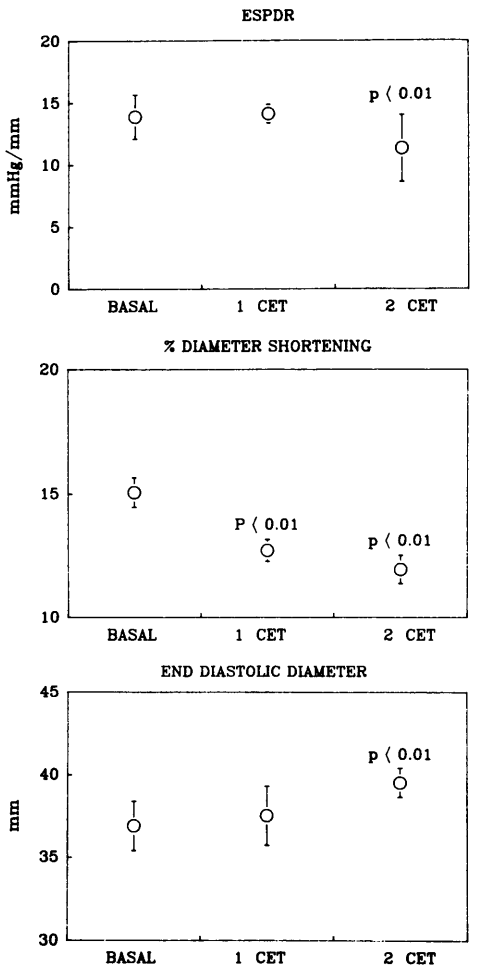

FIG. 2. End-systolic pressure–diameter relationship, % diameter-shortening, and end-diastolic diameter during the basal state and Days 1 and 2 of chronic endotoxemia (CET) in 8 pigs. Data and statistical presentation as in Fig. 1. ESPDR was significantly decreased on Day 2 CET whereas % diameter-shortening (an estimate of ejection fraction) was reduced significantly on both endotoxemic days. End-diastolic diameter was elevated on the second endotoxemic day.

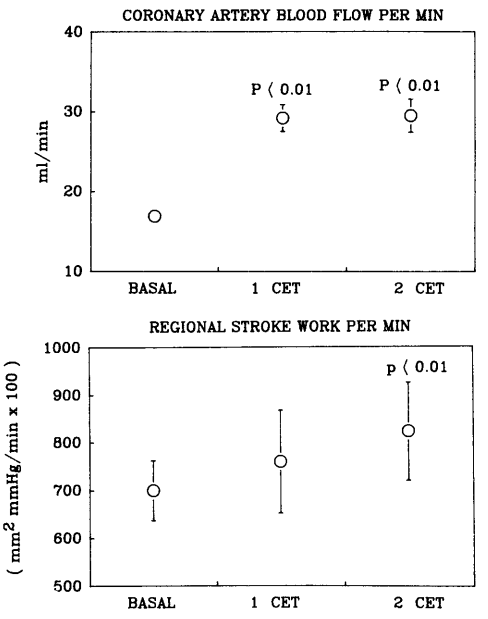

FIG. 3. Coronary artery blood flow and cross-sectional stroke work expressed per minute during the basal state and Days 1 and 2 of endotoxemia in 8 pigs. Minute coronary flow was significantly elevated on both endotoxemic days while cross-sectional minute work was elevated on the second endotoxemic day. Cross-sectional stroke work was calculated from diameter and pressure data (see Methods for details). Data and statistical presentation as in Fig. 1.

flow/work was significantly increased during endotoxemia. This ratio was calculated on a per beat basis to normalize for the increase heart rate (see Fig. 1). This ratio increased twofold on endotoxemia Days 1 and 2 (0.459 ± .06 to 1.25 ± .35 to 1.05 ± 1.05 μl/cm^2 mm Hg, respectively, $P < 0.01$ [two-way ANOVA]).

Table I shows the data observed in pigs that did not survive the endotoxin infusion past the morning of the second day. In these animals, heart rate, peak diastolic pressure, + and $-dP/dt$, % diameter-shortening, the slope of ESPDR, and cardiac output all fell significantly ($P < 0.01$, two-way ANOVA). Coronary flow per beat, cross-sectional stroke work per beat and the ratio of coronary flow/work remained unchanged. Only end-diastolic diameter rose significantly. These responses were markedly different from the survivor group, whose peak systolic pressure, heart rate, cardiac output, dP/dt, and coronary flow/work all rose significantly.

Discussion. Our previous studies have shown that reduced ESPDR and % diameter-shortening accompany chronic endotoxemia (3). This study tested the hypothesis that reduced inotropism was caused by reduced myocardial perfusion. The major finding of this study was that the myocardium was overperfused during chronic endotoxemia. This overperfusion was expressed

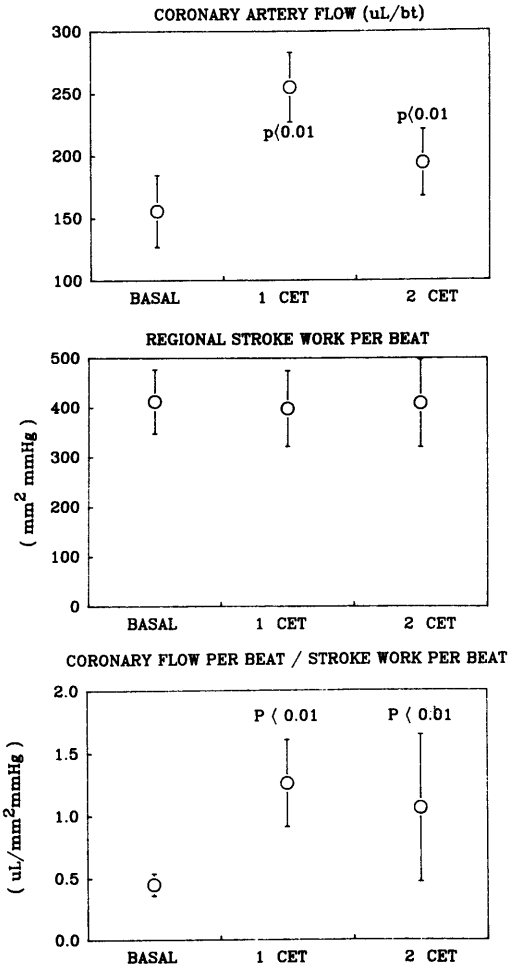

FIG. 4. Coronary blood flow and cross-sectional stroke work expressed per beat and the ratio of flow/work during the basal state and Days 1 and 2 of endotoxemia in 8 pigs. Coronary flow per beat was significantly elevated in both endotoxemic days, whereas cross-sectional stroke work per beat was unchanged. Therefore, the ratio of flow/work was elevated on each endotoxemic day. Data and statistical presentation as in Fig. 1.

TABLE I. HEMODYNAMIC AND CARDIODYNAMIC VARIABLES FROM NONSURVIVING CHRONIC ENDOTOXEMIA PIGS (n = 4)

	Basal	1 CET	
Heart rate (bpm)	117 ± 1.4	103 ± 2.5	$P < 0.01$
Peak LVP systemic pressure (mm Hg)	118 ± 3.0	111 ± 1.3	$P < 0.01$
$+dP/dt_{max}$ (mm Hg/sec)	1693 ± 17	1463 ± 14	$P < 0.01$
$-dP/dt_{max}$ (mm Hg/sec)	2102 ± 20	1736 ± 22	$P < 0.01$
$D - ED$ (mm)	36.4 ± 0.6	40.9 ± 0.8	$P < 0.01$
Diameter-shortening (%)	15.2 ± 0.3	12.1 ± 0.6	$P < 0.01$
ESPDR (mm Hg/mm)	17.6 ± 0.7	11.9 ± 0.5	$P < 0.01$
Cardiac output (liters/min)	2.54 ± 0.06	2.21 ± 0.06	$P < 0.01$
Cross-sectional stroke work per beat	481 ± 7.1	425 ± 9.8	NS
Coronary blood flow (μl/bt)	101 ± 4	90 ± 4	NS
Coronary flow/work	219 ± 80	210 ± 84	NS

Note. $D - ED$, short axis diameter at end diastole; diameter-shortening (%), $[(D - ED) - (D - ES)/D - ED \times 100]$; Cross-sectional stroke work, $\int(\pi D/2)^2/dP$. ESPDR, the slope of the end-systolic pressure–diameter relationship. Four pigs were studied using 10 observations per animal per day. Values are means ± 1 SEM. Statistical analyses were conducted by two-way analysis of variance.

as increased flow/minute, flow per beat, and most importantly, flow-to-work ratio (Fig. 4).

The relationship between cardiac mechanical function and perfusion during models of sepsis and other shock states has been studied. Seigel and Downing in 1970 (9) first explored the possibility that reduced coronary perfusion could be the cause of reduced myocardial inotropism in hemorrhagic shock. They concluded that the maintenance of coronary perfusion, along with buffering metabolic acidosis, was a major therapeutic intervention that promised to maintain cardiac mechanical function in hemorrhagic shock. Hinshaw *et al.* (10) studied acute endotoxemia induced by bolus infusion of endotoxin and concluded that loss of coronary perfusion pressure was responsible for inadequate perfusion and the consequent depression of myocardial contractile state. However, it is expected that coronary flow is reduced during acute endotoxemia, because the marked and sustained arterial hypotension is below the limit of coronary autoregulation. Additional difficulties exist in interpreting these acute studies. Anesthetics, especially barbiturates, impose a significant cardiodepressant action. Moreover, bolus administration of endotoxin in an overwhelming dose is unlike clinical sepsis in that it induces low cardiac output, reduces arterial blood pressure, and occurs rapidly. Clinical systemic sepsis is the constant release of small amounts of bacteria into the circulation which induces high cardiac output and normal or elevated arterial blood pressures, and extends over days.

Studies which mimic the low dose, long-term nature of systemic sepsis have reported coronary vasodilation (11–13). Rumsey *et al.* (12) studied coronary vascular tone of hearts removed from rats subjected to sublethal endotoxin in a Langendorff preparation. He found that coronary vascular tone was significantly lower in hearts from endotoxemic rats. Cunnion *et al.* (13) reported the effect of systemic sepsis on coronary flow and cardiac performance in 7 patients. These septic patients had coronary flows similar to or higher than those of control subjects, a narrowed arteriovenous O_2 difference, and, thus, a lowered O_2 extraction fraction. Furthermore, Cunnion *et al.* reported no net cardiac lactate production or increased O_2 delivery. Thus, they concluded that global myocardial ischemia was not a cause of reduced myocardial inotropism in human systemic sepsis. Our findings are similar to those of Cunnion *et al.*, which implies that the model of sepsis we employed is appropriate to study the mechanisms of reduced myocardial inotropic state in sepsis.

Arterial hypoxia would induce myocardial hyperperfusion at unaltered work rates and can be considered an alternative explanation of these results. Two lines of evidence reject this mechanism: (i) the surviving pigs gener-

ally did not exhibit signs of pulmonary edema coincident with increased coronary flow/work ratios; and (ii) we measured arterial PO_2 in 3 surviving endotoxemic pigs and found no significant decrease. The nonsurvivors exhibited unaltered coronary flow/work ratios, although some of them did exhibit signs of pulmonary edema. Additionally, Cunnion *et al.* (13) reported that increased myocardial O_2 delivery was a feature of human systemic sepsis.

The mechanism of the relative hyperperfusion of the myocardium in chronic endotoxemia can be either the removal of a tonic vasoconstrictor influence or the creation of a coronary vasodilator. The best candidate for the former mechanism is the removal of tonic α-adrenergic receptor activation. Huesch and Duessen (14) demonstrated tonic α-adrenergic tone in the myocardium; its removal increased coronary flow by 15–30%. It seems unlikely, however, that this minor factor can explain the twofold increase in coronary flow/work ratios observed in these endotoxemic pigs. Active vasodilation can be induced by several mechanisms, including activation of both β_1-adrenergic receptors and nonadrenergic vasodilator substances (e.g., acetylcholine, VIP, histamine, dopamine, purines, serotonin, or substance P) (15). The role of endothelial cells in regulating flow is becoming recognized; these cells can produce prostacyclin and/or endothelium-derived relaxing factor (tentatively identified as nitric oxide, NO) (16), both of which cause vasodilation. However, the mechanisms responsible for the hyperperfusion induced by chronic endotoxemia remain to be elucidated.

The major finding of this study was the coincidence of high perfusion and low inotropism during chronic endotoxemia. The coincidence between high perfusion and low inotropism has also been observed during reperfusion following transient ischemia suggesting that the mechanisms may be analogous. It is generally accepted that the loss of contractile function during reperfusion of the ischemic myocardium is mediated by the toxic effects of free radical oxygen species generated by activated neutrophils, formation of xanthine dehydrogenase, and other intracellular mechanisms (reviewed in (17)). Since endotoxin directly stimulates neutrophils to generate free radical oxygen species and release proteolytic enzymes *in vitro* and *in vivo,* it may be likely that endotoxin-stimulated neutrophils, generating reactive oxygen species, mediate cardiac injury during chronic endotoxemia. Indeed, myocardial glutathione, a major intracellular antioxidant, is depleted during chronic endotoxemia (Lee *et al.*, unpublished results).

Conclusion. This study revealed the coincidence of reduced inotropism and augmented perfusion during chronic endotoxemia. The increase in coronary flow was more than double the spontaneous work rate. The mechanism responsible for this increase in coronary blood flow, well over the flow rate necessary to support cardiac work, remains to be determined.

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