Biphasic changes in left ventricular function during hyperdynamic endotoxemia

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Ishihara, Satoshi; John A. Ward, Osamu Tasaki, Basil A. Pruitt, Jr., Martine A. Avors, Richard A. Cassidy and David W. Mozingo. Biphasic changes in left ventricular function during hyperdynamic endotoxemia. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R1516-R1524, 1999.—Cardiac contractility was studied in a clinically relevant conscious swine model simulating human hemodynamics during endotoxemia. The slope of the end-systolic pressure-volume relationship (end-systolic elastance \( E_{ES} \)) was used as a load-independent contractility index. Chronic instrumentation in 10 pigs included two pairs of endocardial ultrasonic crystals for measuring internal major and minor axial dimensions of the left ventricle, a micromanometer for left ventricular pressure measurement, and a thermodilution pulmonary artery catheter. After a 10-day recovery period, control measurements of cardiac hemodynamic function were obtained. The following week, Escherichia coli endotoxin (10 \( \mu \)g·kg \(^{-1} \)·h \(^{-1} \)) was administered intravenously for 24 h. \( E_{ES} \) increased 1 h after endotoxin infusion and decreased beyond 7 h. The later hemodynamic changes resembled human cardiovascular performance during endotoxemia more closely than the changes during the acute phase. \( E_{ES} \) decreased in the later phase. A similar biphasic response of \( E_{ES} \) has been reported during a tumor necrosis factor-\( \alpha \) (TNF) challenge. Even though plasma TNF was highest at 1 h and declined thereafter in this study, no consistent relationship between TNF and \( E_{ES} \) was identified, and TNF levels did not correlate directly with the changes in \( E_{ES} \). 

contractility; tumor necrosis factor-\( \alpha \); endotoxin; hemodynamics; left ventricle

A VARIETY OF STUDIES have shown that during sepsis there are numerous abnormalities in cardiovascular dynamics. Although it is known that myocardial performance is depressed late in the course of sepsis, whether there is impairment of cardiac contractility at the onset of sepsis has not been established. Assessment of this phenomenon is made difficult by the fact that patients with sepsis may be hyperdynamic, with high cardiac output, low systemic vascular resistance, and tachycardia. In addition, these patients may have pulmonary hypertension and may require large infusions of intravascular fluid. Other investigators (35), using high-volume fluid infusion and conventional pressure and flow indexes to evaluate cardiovascular function, have succeeded in reproducing the systemic hyperdynamic changes of sepsis in a porcine model. However, indexes such as cardiac output and arterial pressure are affected by venous return and peripheral resistance as well. To evaluate the pump function of the heart, it is essential to have a specific contractile index that is not sensitive to loading conditions, because both preload and afterload may change dramatically during sepsis. Under these circumstances, repeated measures of myocardial performance could provide additional insight into this problem.

End-systolic elastance \( (E_{ES}) \) is defined as the slope of the end-systolic pressure-volume relationship \( (ESPVR) \) and is a load-independent index of cardiac contractility (37). We have evaluated left ventricular \( (LV) \) contractile function using \( E_{ES} \) in a conscious swine model of endotoxemia that reproduced the hyperdynamic cardiovascular changes \( (i.e., high cardiac output and low peripheral vascular resistance) \) observed in fluid-resuscitated septic patients. The swine was chosen because of its similarity to humans with respect to cardiac physiology. The effect of endotoxemia on the swine cardiovascular system has also been shown to closely resemble the pathophysiological response observed in humans (43). Tumor necrosis factor-\( \alpha \) (TNF) was measured because it has been reported that intravenous TNF produced a cardiovascular response similar to that evoked by intravenous endotoxin (26), which suggested that TNF may mediate the systemic hemodynamic response in sepsis. In addition, several investigators have reported that TNF alters cardiac contractility (24, 31, 32, 41). Whether the in vivo changes in contractility are a direct effect of TNF or mediated indirectly has not been determined. If \( E_{ES} \) changes concurrently with TNF levels, and if the changes are proportional, it would support the notion that this cytokine is a direct mediator of changes in myocardial performance.

The primary purpose of this study was to define the changes in \( E_{ES} \) in a clinically relevant conscious swine model simulating the cardiovascular response of treated patients during sepsis. The secondary purpose was to determine if there is a temporal and quantitative correlation of myocardial performance and plasma TNF levels.

MATERIALS AND METHODS

Ten adult female Yorkshire swine weighing 28.9–41.8 kg were studied. All animals were housed in covered outdoor runs, fed water and standard laboratory chow ad libitum, and observed for 2 wk before use to exclude the presence of preexisting disease. After this observation period the animals were starved for 24 h before instrumentation.

Surgical procedure. The surgical preparation and the hemodynamic data acquisition system have been reported elsewhere (15). The animals were sedated with atropine (0.08 mg/kg), ketamine (2.2 mg/kg), and xylazine (2.2 mg/kg) administered intramuscularly. An endotracheal tube was inserted, and anesthesia was induced with a mixture of isoflurane, nitrous oxide, and oxygen. All animals were administered cefazolin (500 mg iv) daily beginning preopera-
tively until the day of the experiment. Under sterile conditions, polyethylene catheters were placed in the left common carotid artery for blood sampling and the measurement of arterial pressure. One radiopaque sheath introducer (8.5 Fr; American Edwards Laboratories, Irvine, CA) was inserted into the left external jugular vein. A Swan-Ganz thermodilution catheter (7 Fr; American Edwards Laboratories) was inserted through the sheath. The left internal jugular vein was cannulated with a flexible catheter for infusing fluid and endotoxin. A left thoracotomy was performed through the fifth intercostal space. A pneumatic occluder (vascular occluder; In Vivo Metric, Mealsburg, CA) was placed around the inferior vena cava (IVC). The pericardium was opened. A micromanometer (P5; Konigsberg Instruments, Pasadena, CA) was implanted through a small incision in the apex of the left ventricle to measure intracavitary pressure continuously. A pair of crystal ultrasound dimension transducers (internal ventricular transducer pair, 4.0-mm ID; 3-2; Triton Technology, San Diego, CA) were implanted on the LV endocardium adjacent to the anterior and posterior descending coronary arteries to measure the internal LV anteroposterior minor axis diameter. Another pair of the crystals was also placed on the endocardium to measure base-apex major axis diameter. The crystals were monitored with an oscilloscope (2236A; Tektronix, Pittsfield, MA) to ensure that the signals were satisfactory and that the placement of crystals was appropriate. All catheters were exteriorized dorsally. The pericardium was left open, and the chest was closed in layers after the IVC was transiently occluded. LV volume (VLV) was measured during an intravenous catheter occlusion in 1 animal. LVP and LVV, left ventricular (LV) pressure and volume, respectively; ESP, end-systolic pressure; ESPVR, end-systolic pressure-volume relationship; P-V loop, pressure-volume loop; AoP, aortic pressure; PAP, pulmonary arterial pressure; HR, heart rate; CO, cardiac output; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; MPAP, mean pulmonary arterial pressure; CVP, central venous pressure; PVR, pulmonary vascular resistance; V_E, LV end-diastolic volume; V_E, LV end-systolic volume; SVI, stroke volume index; dP/dt, rate of change of LV pressure with respect to time; D_0, x-intercept of ESPVR.

Hemodynamic data acquisition and blood sampling. We have modified the data acquisition system, which has been described previously (42). The crystals were connected to a sonomicrometer (120–1001; Triton Technology), and the signals were amplified. Signals were continuously monitored on an oscilloscope. The Swan-Ganz catheter and the arterial catheter were connected to pressure transducers (P23 ID Statham; Gould, Oxnard, CA). Pressure signals, including that from the LV transducer, were amplified through pressure processors (pressure processor 20–4625–526611; Gould). All dimension and pressure signals were preprocessed (V-Store; Racal Recorders, Hythe Southhampton, UK) and digitized (DA516; Keithley Metrabyte data acquisition system, Tauton, MA). The signals were sampled automatically with custom software for 10 s at 30-s intervals on an IBM-compatible personal computer (Compaq Desk Pro 566s). Figure 1 shows a typical sample output display of V_E measured from one animal during IVC occlusion. Cardiopulmonary measurements were recorded before infusion and at 1, 2, 4, 7, 12, 18, and 24 h postinfusion.

At the end of 24 h, surviving animals were killed. Adequate placement of the crystals was confirmed by necropsy. The digitized data were analyzed for the following hemodynamic parameters, using customized software employed to capture signals: heart rate (HR), cardiac index (CI), MAP, systemic vascular resistance index (SVRI), mean pulmonary artery pressure (MPAP), pulmonary vascular resistance index (PVRI), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), LV end-diastolic volume (V_ED), and LV end-systolic volume (V_ES). CI and SVRI were calculated using standard formulas. With the use of the thermodilution catheter, stroke volume index (SVI) was calculated according to the equation

$$SVI = CI/HR$$

LV ejection fraction (EF) was calculated from the dimension transducer data using the equation

$$EF = V_{ES}/V_{ED}$$

The ESPVR was obtained from the LV pressure-volume loops while the IVC was transiently occluded. LV volume (V_LV) was calculated as

$$V_{LV} = (4\pi/3)(D_{min}/2)^2(D_{maj}/2) = \pi(D_{max})^2(D_{maj})/6$$

where D_max for the dimensions of the minor and the major axes of the left ventricle and D_maj for the major axis of the left ventricle.

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$$V_{LV} = (4\pi/3)(D_{min}/2)^2(D_{maj}/2) = \pi(D_{max})^2(D_{maj})/6$$

where D_min is a dimension of the minor axis of the left ventricle, and D_maj is a dimension of the major axis of the left ventricle.
Table 1. Cardiopulmonary hemodynamics at baseline

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Sepsis</th>
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<tbody>
<tr>
<td>HR, beats/min</td>
<td>132 ± 19</td>
<td>109 ± 16*</td>
</tr>
<tr>
<td>CI, l·min⁻¹·m⁻²</td>
<td>6.84 ± 1.08</td>
<td>5.91 ± 0.70</td>
</tr>
<tr>
<td>SVI, ml/m²</td>
<td>51.9 ± 6.0</td>
<td>55.8 ± 8.5</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>100.4 ± 7.0</td>
<td>108.3 ± 8.5</td>
</tr>
<tr>
<td>MPAP, mmHg</td>
<td>1156 ± 194</td>
<td>1421 ± 152*</td>
</tr>
<tr>
<td>SVRI, dyn·s·cm⁻⁵·m²</td>
<td>25.0 ± 5.2</td>
<td>26.8 ± 2.83</td>
</tr>
<tr>
<td>PVRI, dyn·s·cm⁻⁵·m²</td>
<td>2230 ± 56.3</td>
<td>2092.2 ± 51.9</td>
</tr>
<tr>
<td>VEO₂, ml</td>
<td>39.3 ± 17.7</td>
<td>39.7 ± 17.9</td>
</tr>
<tr>
<td>Hct, %</td>
<td>25.7 ± 2.3</td>
<td>27.6 ± 6.0</td>
</tr>
<tr>
<td>EES, mmHg/ml</td>
<td>8.55 ± 5.39</td>
<td>7.79 ± 2.86</td>
</tr>
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Values are means ± SD. HR, heart rate; CI, cardiac index; SVI, stroke volume index; MAP, mean arterial pressure; SVRI, systemic vascular resistance index; MPAP, mean pulmonary artery pressure; PVRI, pulmonary vascular resistance index; VEO₂, left ventricular (LV) end-diastolic volume; Hct, hematocrit; EES, slope of LV end-systolic pressure-volume relationship. *P < 0.05 vs. control.

ES was determined by using a linear regression algorithm to fit a straight line to the end-systolic pressure-volume points according to the formula

$$P_{ES} = EES(V_{ES} - V_0)$$

where $P_{ES}$ is LV end-systolic pressure and $V_0$ is its volume-axis intercept. The LV was occluded no less than three times at each time point with at least 1 min between occlusions and at least a 20-mmHg reduction of $P_{ES}$. End-systolic points in the loop were geometrically defined. The correlation coefficient of the pressure-volume relationship at all measurements was no less than 0.95.

Blood samples were obtained at the same times as hemodynamic data sampling except at 18 h. Plasma TNF was measured with a newly developed porcine-specific two-site ELISA kit (Endogen, Cambridge, MA) with a lower limit of detection of 5.1 pg/ml and assay range of 50–800 pg/ml (5). Plasma epinephrine (Epi) and norepinephrine (NE) were analyzed by HPLC. Analysis of plasma total nitrites has been described previously (22).

Statistical analysis. Data analysis was performed with a Power Macintosh 7100/66 computer (Apple Computer, Cupertino, CA) and a statistical software package (StatView 4.5; Abacus Concepts, Berkeley, CA). Data are presented as means ± SD. In raw data and normalized data sets, statistical analysis between groups was performed with the template for ANOVA with repeated measures. If a significant difference was found, post hoc differences were identified with Scheffé’s test at each time point. In the raw data set, significant time interactions within groups were evaluated with the same template to confirm this result. If a significant difference between times within groups was found, time differences from baseline were assessed by a Student-Newman-Keuls test. P < 0.05 was considered a statistically significant difference.

RESULTS

Three of 10 animals died within 24 h after initiation of the endotoxin. Both control and postendotoxin data obtained from those animals were eliminated in this study. Hemodynamic parameters at baseline are shown in Table 1. HR was higher and SVRI was lower at the baseline of the control period. This statistically significant difference is considered to be the effect of placing the animals in the small cage used for hemodynamic observation in the endotoxin study. This hypothesis is supported by the gradual decrease of HR in the control group thereafter (Fig. 2), which is consistent with adaptation of the animals to those cages. All parameters shown in Figs. 2–5 are normalized to baseline and expressed as a percentage.

In the control period, although HR gradually decreased (Fig. 2), SVI increased (Fig. 4); therefore, there was no significant change in CI and SVRI, whereas MAP was slightly increased (Fig. 3). Endotoxin produced tachycardia and an increase in PVRI (Fig. 2). This was associated with reduced SVRI (Fig. 3). In the initial 2 h, MAP and CI decreased. This initial depression of MAP was accompanied by a decrease in SVRI. During this time period, the decrease in CI appeared to be caused by the combined effect of a reduction of SVI and $V_{ED}$ (Fig. 4). Eight hours after endotoxin infusion began, MAP was the same in both study periods. CI at and after 12 h in the endotoxin study period exceeded CI measured at those times in the control study period. That change in CI was associated with a second reduction of SVRI, which persisted until the end of the study, and a progressive increase in $V_{ED}$, which became significantly greater than control values at 18 and 24 h. $E_{ES}$ increased significantly at 1 h and decreased thereafter, becoming significantly lower than in the control period at 7, 18, and 24 h (Fig. 5). Figure 6 demonstrates the typical changes in $E_{ES}$ at baseline and at 2 and 24 h after endotoxin administration in one animal. Other hemodynamic parameters measured, as well as plasma nitrite throughout the experiment, are shown in Table 2. Although differences in MPAP values were not

![Fig. 2](http://ajpregu.physiology.org/). Time course of HR and pulmonary vascular resistance index (PVRI) during continuous endotoxin infusion. Data are represented as percentage of baseline. Values are means ± SD. *P < 0.05 vs. control; †P < 0.05 vs. baseline.)
statistically significant after 8 h, sepsis values were higher than control values throughout the study, indicating persistent pulmonary hypertension. Pressures related to preload, CVP and PCWP, were not significantly different. Although ANOVA identified a significant difference between groups in VES, further analysis failed to detect which time point was significant. EF and dP/dt were not significantly different in the two study periods, possibly because those indexes are load dependent. There was no significant change in plasma nitrite levels in the sepsis.

Figure 7 depicts TNF levels during sepsis. TNF peaked at 1 h and receded gradually despite continuous infusion of endotoxin. The coefficient of determination (r²) between peak plasma TNF and EES in each animal was 0.334, indicating that the correlation was low. The correlation between peak logTNF and EES was also low (r² = 0.363). When not only peak values but whole data at all measurements (0, 1, 2, 4, 7, 12, and 24 h in each animal) are included, r² values get lower. (r² = 0.19 for TNF vs. EES; r² = 0.0279 for logTNF vs. EES). Plasma concentrations of Epi and NE in the septic state, both Epi and NE increased markedly in the acute phase. Epi values remained high until 12 h, whereas NE levels returned to baseline after 4 h. There was no difference in either group at 24 h. The correlations between TNF and catecholamines were low. TNF vs. Epi and logTNF vs. logEpi r² values were 0.179 and 0.477, respectively. For TNF vs. NE and logTNF vs. logNE, r² was 0.184 and 0.245, respectively.

**DISCUSSION**

We have shown for the first time that, in a model of shock induced by continuous intravenous administration of endotoxin, there is a biphasic pattern of myocardial contractility. In the early period (1 h), contractility, as measured by EES, significantly increased. This occ...
and mortality rate comparable to anesthetized swine. A dose of endotoxin to achieve a hemodynamic response in conscious swine generally need at least five times the dose by the effect of anesthetics or other drugs. However, fully conscious state to obtain data that are not clouded by the mechanisms of endotoxic shock. In developing a model, it is important to select an animal that will mimic the human clinical response and avoid procedures that will add to or detract from the response. Because anesthetic agents induce significant changes in hemodynamics, cardiac contractility (7), and cytokine production (38) and can alter endotoxin clearance by impairing reticuloendothelial function, conscious animals were used in this study. Hand et al. (11) state that an adequate swine endotoxin model requires the characteristic of the human hemodynamic reaction to endotoxin (33), suggesting that the late (after 12 h) hemodynamic changes simulate the human cardiovascular reaction to endotoxin (33), suggesting that the late (after 12 h) hemodynamic changes simulate the human cardiovascular reaction to endotoxin (33), suggesting that the late (after 12 h) hemodynamic changes simulate the human cardiovascular reaction to endotoxin (33), suggesting that the late (after 12 h) hemodynamic changes simulate the human cardiovascular reaction to endotoxin (33), suggesting that the late (after 12 h) hemodynamic changes simulate the human cardiovascular reaction to endotoxin (33), suggesting that the late (after 12 h) hemodynamic changes simulate the human cardiovascular reaction to endotoxin (33)
A variable pattern of early $E_{ES}$ response has been reported by other investigators using different models of sepsis. The biphasic changes we observed, which were an early increase and a delayed decrease of $E_{ES}$, have not been reported before. The depression of the contractility during the later phase of the endotoxin study period is consistent with the reduction of $E_{ES}$ during chronic endotoxemia as observed in earlier studies, which used the dog (34, 39), the sheep (29), and the pig (20). The early increase in $E_{ES}$ that we observed was also noted by Kober et al. (17) in acutely prepared dogs. Because cardiac performance in the later phase of the endotoxin period in this study is analogous to the clinical situation, depression of $E_{ES}$ appears to be a better representation of the contractile status in patients with established sepsis than the early increase in $E_{ES}$. The acute elevation of contractility and other hemodynamic changes observed at the early phase in this model are not observed in humans when sepsis is definitively diagnosed. Whether the later decrease is predicted by an early increase in contractile performance is not known. However, if an early increase in contractile performance is a harbinger of subsequent contractile depression, more aggressive clinical attention to this phenomenon may be worthwhile and may have significant importance: defining early increases in contractility could indicate the need for aggressive management, because subsequent decreases in cardiac performance may follow. Work remains to be done to define whether these patterns of myocardial performance are mechanistically linked.

Although the decrease in SVRI in the early phase appeared similar to the cardiovascular response usually observed in septic human patients, the changes in $V_{LV}$ were not. Whether those changes occur in humans is unknown, but it is possible that they might be missed in clinical settings because they were transient in the extremely acute phase of sepsis. The brief duration of those changes early in the endotoxin study period raises the possibility that they may go undetected in patients and other animal models in which measurements are made after sepsis is established. The later phase changes during the endotoxin study period raise the possibility that they may go undetected in patients and other animal models in which measurements are made after sepsis is established. The later phase changes during the endotoxin study period, which closely resemble those of clinical sepsis, make our model clinically relevant. The two-phase character of this model will permit systematic examination of the pathophysiological mechanisms of septic shock, and the characteristics of the late phase make it particularly useful as a reproducible analog of clinical sepsis for the evaluation of therapeutic interventions.

In the acute phase of the endotoxin study period, there was a significant decrease in MAP without any statistically significant changes in filling pressure as indicated by CVP and PCWP. However, measurement of $V_{ED}$ revealed a reduction in preload that was not accounted for by the pressure measurements. It has been reported that PCWP does not follow left atrial pressure or $V_{ED}$, which are more accurate indexes of LV preload, during sepsis (18). This dissociation is presumed to be caused by precapillary vasoconstriction in response to hypoxia because it is occasionally observed in patients suffering from nonspecific respiratory failure as well as in those with sepsis (21).

Many investigators have reported that TNF challenge induces hemodynamic changes similar to endotoxin. TNF is reported to be promptly cleared from the plasma (1). In this study, the plasma concentration of TNF decreased despite continuous endotoxin infusion as previously described by others in a sheep model (28). These results suggest that the time course of the initial change in hemodynamics is comparable to that induced by a bolus injection of recombinant TNF as used in other studies. Murray and Freeman (24) reported TNF-induced biphasic changes in $E_{ES}$ and other indexes of LV contractility. Pagani and colleagues (31, 32) demon-
strated that preload recruitable stroke work, another load-independent contractility index, increased in the acute phase and decreased in the chronic phase. Our results closely resemble theirs.

The fact that both endotoxin and TNF induce biphasic changes in cardiac contractility is consistent with a shared common pathway that leads to impairment of LV function. Whether TNF is a direct mediator impairing LV function has not been resolved. In some in vitro studies, TNF has been found to have a negative inotropic effect on cardiomyocytes (8, 19), but the dose of TNF used in those studies may have exceeded the physiological concentration of plasma or tissue TNF. Anti-TNF antibody reverses certain changes in cardiovascular performance induced by endotoxin, such as those of CI and MAP (16, 23, 25), but there is disagreement as to whether anti-TNF antibody prevents impairment of LV contractility (12, 27). In this study $E_{ES}$ increased when plasma TNF level peaked at the very acute phase and decreased thereafter when TNF returned to the normal range. There was some delay in cardiac dysfunction after the TNF surge, and no significant correlation between plasma TNF and $E_{ES}$ was found. These results suggest that TNF is produced and cardiac function is impaired in response to endotoxin, but there might be some intermediate factor or process between TNF production and the decrease in $E_{ES}$. TNF appeared to be associated with an increase in cardiac contractility, because both phenomena occurred simultaneously immediately after the endotoxin infusion began.

$E_{ES}$ showed no significant correlation with peak or overall plasma TNF. There are two possible explanations. First, cardiac contractility does not normally depend on plasma TNF levels, but it may be altered if TNF exceeds a threshold. Second, cardiac contractility is influenced by other factors, such as sympathogenic effects. Administration of endotoxin caused a marked catecholamine release. However, the correlation between plasma TNF and catecholamine levels was low. Our catecholamine data support the hypothesis that the effects of those agents contributed to a relatively weak correlation between TNF and $E_{ES}$. Further study employing inhibition of TNF remains to be done to test this hypothesis.

The mechanism causing the biphasic change of $E_{ES}$ is undefined. Although the release of catecholamines has the potential to increase $E_{ES}$ in the acute phase of study, pretreatment with propranolol failed to prevent an increase in $E_{ES}$ after administration of TNF to a canine model, in which a pacemaker was implanted to keep HR constant (24). This result suggests that there might be some mechanism, including TNF itself, other than autonomic action that causes the acute increase in contractility. Several factors may be involved at the later phase of reduced contractility. Coronary insufficiency, oxygen free radical generation, and nitric oxide production have all been implicated. Goldfarb et al. (9) reported a significant increase in coronary perfusion while stroke work remained unchanged in the endotoxic pig, and other studies have identified a dissociation between myocardial depression and coronary insufficiency (4). Few studies support a decrease of coronary flow in sepsis. Oxygen free radicals are believed to play a major role in tissue injury of the heart (2). It is known that endotoxin stimulates TNF production and that both endotoxin and TNF stimulate neutrophils to release oxygen radicals (6). We have reported that superoxide production by the granulocytes was suppressed at 24 h after initiation of endotoxin infusion (14). Another study suggests that endotoxin activates granulocytes several hours after endotoxin infusion (40). It has also been reported that a chain of reactions progresses from endotoxin-induced release of TNF and oxygen radical production (3) to myocardial injury caused by free radicals (9). The time course of the results in the current study are consistent with such a sequential process, which may account for the delayed decrease in contractility. We measured nitrite, which is the intermediate metabolite of nitric oxide, but failed to find evidence supporting a role for nitric oxide in this phenomenon. Other proposed factors include myocardial depressant factor, structural disorder of the myocyte, and myocardial edema, but none of these have been confirmed as clinically important.

In summary, myocardial LV end-systolic contractility, as indexed by $E_{ES}$, exhibited a biphasic change in endotoxin-infused conscious swine. Contractility increased immediately after endotoxin infusion and decreased subsequently in association with changes in hemodynamic indexes consistent with clinical sepsis. These results indicate that end-systolic contractility was diminished during chronic endotoxemia and demonstrate that the delayed functional impairment of the cardiovascular system is not prevented by fluid resuscitation. In this model, circulating levels of TNF were highest 1 h after the initiation of endotoxin, at which time $E_{ES}$ increased, but CI, MAP, SVRI, $V_{ED}$, and SVI were all depressed. TNF levels had decreased by the time the circulatory changes characteristic of sepsis appeared.

Perspectives

$E_{ES}$ increased after 1 h of endotoxin infusion, and TNF peaked at the same time. $E_{ES}$ was below the baseline after 8 h, whereas TNF returned to the baseline after 12 h of endotoxin infusion. Because other late-phase hemodynamics resembled human sepsis, reduced $E_{ES}$ may also be representative of human sepsis. The delay between TNF release into the circulating blood and the decrease in $E_{ES}$ is consistent with an indirect or intermediate counterregulatory mechanism.

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Department of the Army or the U.S. Department of Defense.

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