Gram-negative Bacteremia Produces Both Severe Systolic and Diastolic Cardiac Dysfunction in a Canine Model That Simulates Human Septic Shock

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Abstract

A canine sepsis model that simulates the human cardiovascular response to septic shock was produced in 10 conscious unsedated dogs by implanting an *Eschichia coli*-infected clot into the peritoneum, resulting in bacteremia. By employing serial, simultaneous measurements of radionuclide scan-determined left ventricular (LV) ejection fraction (EF) and thermodilution cardiac index (CI), the end-diastolic volume index (EDVI) was calculated (EDVI = stroke volume index ÷ EF). By using three different methods of quantifying serial ventricular performance (EF, shifts in the Starling ventricular function curve using EDVI vs. stroke work index, and the ventricular function curve response to volume infusion), this study provides evidence ($P < 0.01$) that septic shock produces a profound, but reversible, decrease in systolic ventricular performance. This decreased performance was not seen in controls and was associated with ventricular dilatation ($P < 0.01$); the latter response was dependent on an adequate volume infusion. Further studies of EDVI and pulmonary capillary wedge pressure during diastole revealed a significant, though reversible, shift ($P < 0.001$) in the diastolic volume/pressure (or compliance) relationship during septic shock.

Introduction

Shock secondary to sepsis has become one of the most frequent causes of morbidity and mortality in clinical medicine, despite the availability of highly potent antibiotic regimens (1, 2). Septic shock has become the most common cause of death in intensive care units in the United States (3–5). A better understanding of the pathogenesis of the septic shock syndrome can lead to more effective treatment regimens (6); however, septic shock in humans is difficult to study because the disease is very serious with a high mortality (1, 2). Thus, septic shock must be treated with state-of-the-art fluid and pharmacologic therapy as soon as possible. These limitations on human investigation make it imperative to develop an animal model of septic shock to investigate more fully the treatment and pathogenesis of this highly lethal syndrome.

Most animal models of septic shock do not produce a cardiovascular profile similar to that seen in humans (3, 7). Recent studies of human septic shock have shown clearly that the most common initial cardiovascular pattern consists of a high cardiac index (CI),[1] a decreased systemic vascular resistance index (SVRI), and a normal or low measure of preload, most commonly expressed clinically as a decreased pulmonary capillary wedge pressure (PCWP) (7–15). In a recent evaluation of septic shock patients (16), these hemodynamic parameters were further defined by performing simultaneous measurements of radionuclide-gated blood pool scans along with the intravascular catheter-derived hemodynamic parameters. These latter studies provide strong evidence that most septic shock patients develop a decreased left ventricular (LV) ejection fraction (EF) and dilatation of the left ventricle, along with the increased CI and decreased SVRI and PCWP described above. Furthermore, it is important to realize that these cardiovascular evaluations were performed on humans who were receiving a large amount of fluid replacement in order to increase the mean arterial pressure (MAP) to the normal range.

Animal models of sepsis have frequently employed a large lethal dose of intravenous endotoxin or live bacteria which resulted in an animal's death in 3–6 h. This model produced a low CI and high SVRI, a hemodynamic pattern not typical of that seen in humans. In these studies, the animal would usually receive no (or only maintenance) fluid therapy and would die within a few hours with a very low CI. This is a temporal pattern that was rarely seen with humans (3, 7, 17–27).

In the present study, a canine model of septic shock was modified with the purpose of simulating, as closely as possible, the cardiovascular dysfunction seen with human sepsis. A recently developed animal model was utilized where live Gram-negative bacteria were introduced into the peritoneal cavity in a fibrin clot as a nidus of infection resulting in sustained bacteremia (28). Serial determinations of both intravascular catheter-determined hemodynamics and simultaneous radionuclide cineangiograms were performed in conscious unsedated animals to evaluate fully the systolic and diastolic ventricular function in the absence of the effects of anesthesia. The animals were

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Portions of this work were presented at the National Meeting of the American Federation for Clinical Research, Washington, DC (1985).

The opinions and assertions contained in this article are the private ones of the authors, are not to be construed as official, or reflecting the views of the Armed Forces of the United States of America. The experiments reported herein were conducted according to the principles set forth in the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council, Department of Health, Education and Welfare, Publication No. 74-23 (National Institutes of Health).

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Received for publication 19 September 1985 and in revised form 18 February 1986.

The Journal of Clinical Investigation, Inc.
Volume 78, July 1986, 259–270

1. *Abbreviations used in this paper:* CI, cardiac index; CO, cardiac output; CVP, central venous pressure; EDVI, end-diastolic volume index; EF, ejection fraction; ESVI, end-systolic volume index; HR, heart rate; LV, left ventricular; LVSWI, left ventricular stroke-work index; MAP, mean arterial pressure; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; SVI, stroke volume index; SVRI, systemic vascular resistance index; VI, volume infusion.

evaluated before and after volume challenge to simulate fully the human clinical course. This study demonstrates that this model simulates both the "hyperdynamic" state and the severe reversible myocardial decrease in EF, a profile that had been previously described in humans (16). This study also demonstrates the role of fluid therapy in producing this abnormal cardiovascular pattern, and provides further insight regarding the systolic and diastolic ventricular dysfunction evidenced during bacteremia.

Methods

Experimental design. The protocol followed in these experiments is shown in Fig. 1. Employing only local anesthesia with 1% lidocaine, femoral and pulmonary artery catheters were placed in awake animals at 1 wk prior to surgery to obtain hemodynamic and laboratory data at the baseline time point. Blood was cultured and routine laboratory tests performed (please see subsection "Laboratory data"). In conscious animals, simultaneous hemodynamic data was obtained from both intravascular catheters and the gated-radionuclide cineangiogram of the LV. The animals then received a volume infusion (VI) (see below), and complete hemodynamic and radionuclide studies were repeated. This comprehensive evaluation was performed in 60–120 min and all catheters were then removed. Surgery was performed at day 0 with placement of a clot, either sterile (control) or infected. The comprehensive evaluation initially performed at baseline was repeated at days 1, 2, and 10.

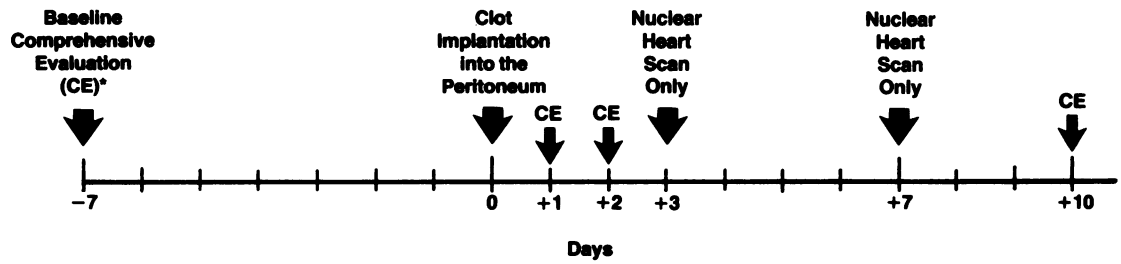
Surgical procedure. Sixteen 2-yr-old male beagles weighing a mean±SEM of 12.5±0.4 kg were used in these experiments. Animals had free access to water and food throughout the study, except for the 12 hours preoperatively, i.e., prior to surgical implantation of a sterile or infected clot into the peritoneum (see below). Anesthesia was induced with sodium pentobarbitol (20 mg/kg) and maintained with spontaneous ventilation via an endotracheal tube with 1% halothane and 100% oxygen. An upper abdominal midline laparotomy was performed, using aseptic technique. Bacterial peritonitis was induced in 10 dogs by implanting into the abdominal cavity a fibrin-thrombin clot containing viable *Escherichia coli.* A sterile fibrin-thrombin clot was implanted into the abdomen of six control dogs. After implantation of the infected or sterile clot, the incision was sutured closed and dressed. Please note that no cardiovascular evaluation was performed in close proximity to this general anesthesia and surgery (see Fig. 1) because anesthesia and surgery may alter cardiovascular function.

Preparation of fibrin clot. The clots were prepared as previously described (28). Briefly, the clots were made from a 1% solution (wt/vol) of bovine fibrinogen (Sigma Chemical Co., St. Louis, MO) in sterile saline. The volume of fibrinogen solution was adjusted according to the weight of the dog (10 ml/kg). The fibrinogen was sterilized by passage through 0.02-μm Nalgene filters. The calculated dose of bacteria (see below), suspended in 10 ml of saline, was added to the fibrinogen solution and mixed with a magnetic stirrer. The clot was formed by adding human thrombin (5 U/ml fibrinogen solution) to the above solution and the resulting mixture was incubated at room temperature for 30 min.

The strain of *E. coli* used in these studies was provided by Dr. Lerner B. Hinshaw and was originally isolated from a patient with urinary tract sepsis. The bacteria were stored at −70°C in 1-ml aliquots in brain-heart infusion broth and glycerol. For preparation of an infected fibrin clot, 500 ml of brain-heart infusion was inoculated with a 1-ml aliquot of thawed bacteria. The bacteria were incubated for 18 h, centrifuged, and were then washed twice in sterile saline. The concentration of bacteria in the final suspension was estimated turbidimetrically by comparing the newly grown bacterial suspension to known standards and subsequently bacteria were quantified by plating successive 10-fold dilutions of the bacterial suspension onto MacConkey's agar and scoring visible colonies after 24 h of incubation at 37°C. Based on results in preliminary studies, the target dose was 14×10^9 viable organisms per kilogram of body weight. The actual dose, as calculated by the dilution method outlined above, was a mean±standard error of the mean of $15.5 \pm 0.3 \times 10^9$ organisms per kilogram of body weight.

Placement of catheters. Femoral and pulmonary artery catheters were placed in awake animals using aseptic technique and only local anesthesia (1% lidocaine). A 7.5 French Swan-Ganz thermodilution catheter with a 15-m proximal injection port (Edwards Laboratories, Santa Ana, CA) was introduced through an 8.0 French introducer (Cordis Corporation, Miami, FL) placed percutaneously via the external jugular vein into the pulmonary artery and positioned so that the PCWP could be measured repeatedly with balloon inflation. A 20-gauge × 12.7-cm Teflon catheter (Arrow International, Reading, PA) was introduced percutaneously into the femoral artery. These catheters were placed at four time points: 1 wk prior to surgery (baseline), days 1 and 2 postsurgery when the animals had bacteremia, and 10 days postsurgery when they were recovering (recovery). After performing the hemodynamic profiles, all catheters in each dog were completely removed each day.

Physiologic measurements. All measurements made from indwelling catheters were performed in unanesthetized animals that were resting quietly in slings. Cardiac output (CO) was determined by the thermodilution method, using a Waters TC-2 computer (Waters Instruments, Inc., Rochester, MN). MAP, pulmonary arterial pressure (PAP), central venous pressure (CVP), and PCWP, were measured with transducers (MK-404 DT, Sorenson, Salt Lake City, UT) and recorded on a four-channel recorder (Hewlett-Packard Co., Palo Alto, CA). Heart rate (HR) was determined from the arterial pressure tracings. Serial hemodynamic measurements were made prior to and after infusion of lactated Ringer's solution at a dose of 80 ml/kg body weight given over 1 h at the four following time points: baseline, day 1, day 2, and recovery.



*Comprehensive Evaluation (CE): 1. Conventional hemodynamics using femoral and pulmonary artery catheters.
2. Simultaneous with #1: nuclear heart scan.
3. Laboratory analysis
4. Volume infusion (VI @ 80 ml/Kg/hour)
5. Repeat #1 and #2 Post VI

Figure 1. This schema outlines the experimental design and its time course in the 10 infected clot and the 6 sterile clot (control) dogs.

Radionuclide cineangiography studies. All radionuclide cineangiography studies were performed on unanesthesized animals resting comfortably in a padded cradle. The serial cineangiography studies were performed immediately after hemodynamic data from indwelling catheters, both prior to and following VI at the same four time points noted above.

Radionuclide-gated blood pool scanning was performed employing conventional techniques. Animals received an injection of stannous pyrophosphate, and 30 min later received 30 mCi of technetium-99m to accomplish in vivo labeling of circulating erythrocytes. With the animals in the supine position, the camera was positioned at a 35° left anterior oblique orientation with a 15° caudal tilt to isolate the LV. LV and background regions of interest were labeled, and background-corrected LV time-activity curves were generated over 120–180 s with 125,000 counts per frame for a total of 30 images per heart beat. LV EF was calculated from each curve as EF = (EDC − ESC)/(EDC − Bkgd), where EDC = end-diastolic counts, ESC = end-systolic counts, and Bkgd = background counts.

Hemodynamic calculations. Hemodynamic data were indexed by body weight in kilograms. The CI (milliliters/kilogram per minute) equals the mean (three determinations) cardiac output/weight in kilograms. LV stroke-work index (LVSWI), SVRI, and stroke volume index (SVI) were calculated according to the standard formula: LVSWI (gram-meters per kilogram) = MAP − PAWP × CI × 0.0136/HR, SVRI (dynes · second · centimeter^{-5}/kilogram) = 80 × (MAP − CVP)/CI, and SVI (milliliters per beat/kilogram) = CI/HR. The end-diastolic volume index (EDVI) and end-systolic volume index (ESVI) were calculated from simultaneously obtained hemodynamic studies and radionuclide scans using the formulas: EDVI = SVI (from thermodilution cardiac output)/EF (from radionuclide cineangiography); and ESVI = EDVI − SVI. "Simultaneously obtained" means the scan was quantified from a radionuclide collection during a 2–3-min time period immediately after three to six thermodilution COs were also performed and averaged.

Laboratory data. Blood samples were obtained for laboratory analysis prior to volume infusion at the following time points: baseline, day 1, day 2, and recovery. Laboratory determinations included: arterial blood gases, complete blood count, electrolytes, calcium, glucose, blood urea nitrogen, creatinine, and blood culture. Arterial blood gases were measured at 37°C with a blood analyzer (model 178, Corning Medical, Medfield, MA). A complete blood count was done using an automatic analyzer (model S, plus II, Coulter Electronics blood analyzer, Hialeah, FL). Electrolytes were measured from serum (model 343, Flame Photometer, Instrumentation Laboratories, Cidra, PR, and model 3500, Gilford Instruments chemical analyzer, Oberlin, OH).

Statistics employed in this study. Mean values were compared with the use of the appropriate paired-sample *t* test. The 95% confidence regions shown in Figs. 5 *A* and *B* and 6 were based on Hotelling's T^2-statistic (29). The hatched rectangles shown in Fig. 2 *A* and *B* represent the mean values for 51 normal dogs and the respective standard error (Table I) adjusted to the number of septic dogs (10) and control dogs (6) for purposes of comparison. Two-sample *t* tests were used to compare means of sterile and infected clot dogs and for laboratory data.

In Fig. 7 *A* and *B*, in order to perform appropriate statistical comparisons of the serial time points in sterile and septic clot groups, the average or midpoint of each pre- and post-VI line was calculated by subtracting the pre from the postvalue for EDVI and PCWP for each dog, and dividing in half. Each of these determinations is then added to the respective pre-VI value to obtain the midpoint of each pre- and post-VI line. These EDVI and PCWP values were averaged and are represented by black dots as the midpoints of the gray lines plotted in Fig. 7 *A* and *B*.

Because a major question in these experiments was whether the ventricular volume/pressure relationship was normal at different serial time points in the sterile or septic clot dogs, all serial time points were compared to normal. The normals were represented by both the 10 septic and 6 sterile clot dogs at baseline, i.e., values derived before any surgery or intervention had been performed. Please note that the pressure employed in Fig. 7 was the PCWP during diastole (from the arterial and ECG tracing); however, the diastolic PCWP was the same as the overall and expiratory PCWP in the 16 dogs reported in this study.

Table I. Determination of Hemodynamic Values in 51 Normal Dogs

Hemodynamic value	Mean±SE
Heart rate (*beats/min*)	116±3
Mean arterial pressure (*mmHg*)	130±2
Mean pulmonary artery pressure (*mmHg*)	20±6
Pulmonary capillary wedge pressure (*mmHg*)	8.6±4.2
Right atrial pressure (*mmHg*)	4±0.57
Cardiac index (*ml/kg/min*)	269±9.7
Ejection fraction	0.65±0.01
Stroke volume index (*ml-beat/kg*)	2.31±0.07
Systemic vascular resistance index (*dynes · s · cm^{-5}/kg*)	40.3±1.6
Left ventricular stroke work index (*g-m/kg*)	3.8±0.14
End-diastolic volume index (*ml/kg*)	3.66±0.15
End-systolic volume index (*ml/kg*)	1.34±0.09

Results

Blood cultures and clinical manifestations. For the first 2 d after surgery, all the dogs implanted with a septic clot had uniformly positive blood cultures. In all dogs, the organism grown from the blood was an *E. coli,* the same genus and species as the microorganism that was implanted into the abdomen. The blood cultures were sterile at baseline and recovery. During the first 3 d after surgery, the bacteremic dogs were febrile (Table II) and demonstrated signs of septic shock, i.e., weakness, malaise, and lethargy. However, with no antibiotics or pressor therapy other than infusion of volume, all animals clinically and microbiologically (negative blood cultures) fully recovered within 7–10 d after surgery. The dogs implanted with a sterile clot were afebrile, had negative blood cultures, and appeared healthy throughout the study. Usual therapy with antibiotics, pressors, steroids, etc. was not used in order to simulate untreated septic shock.

Hemodynamics of sepsis. Fig. 2 groups the four commonly employed clinical cardiovascular parameters (MAP, CI, SVRI, and PCWP) used to describe the hemodynamic profile of septic shock. These four parameters are shown in infected dogs (Fig. 2 *A*) and in control dogs (Fig. 2 *B*) on serial days (baseline, day 1, day 2, and recovery). The serial mean values prior to VI are

Table II. Serial Mean Temperatures

	Baseline	Day 1	Day 2	Recovery
	°C	°C	°C	°C
Control dogs $n = 6$	38.13±0.16	38.18±0.15	37.88±0.15	38.17±0.16
Infected dogs $n = 10$	38.30±0.6	38.45±0.17	38.76±0.13*	38.07±0.10

P values resulted from paired-sample *t* tests comparing means from days 1, 2, or recovery to baseline.
* $P < 0.01$.

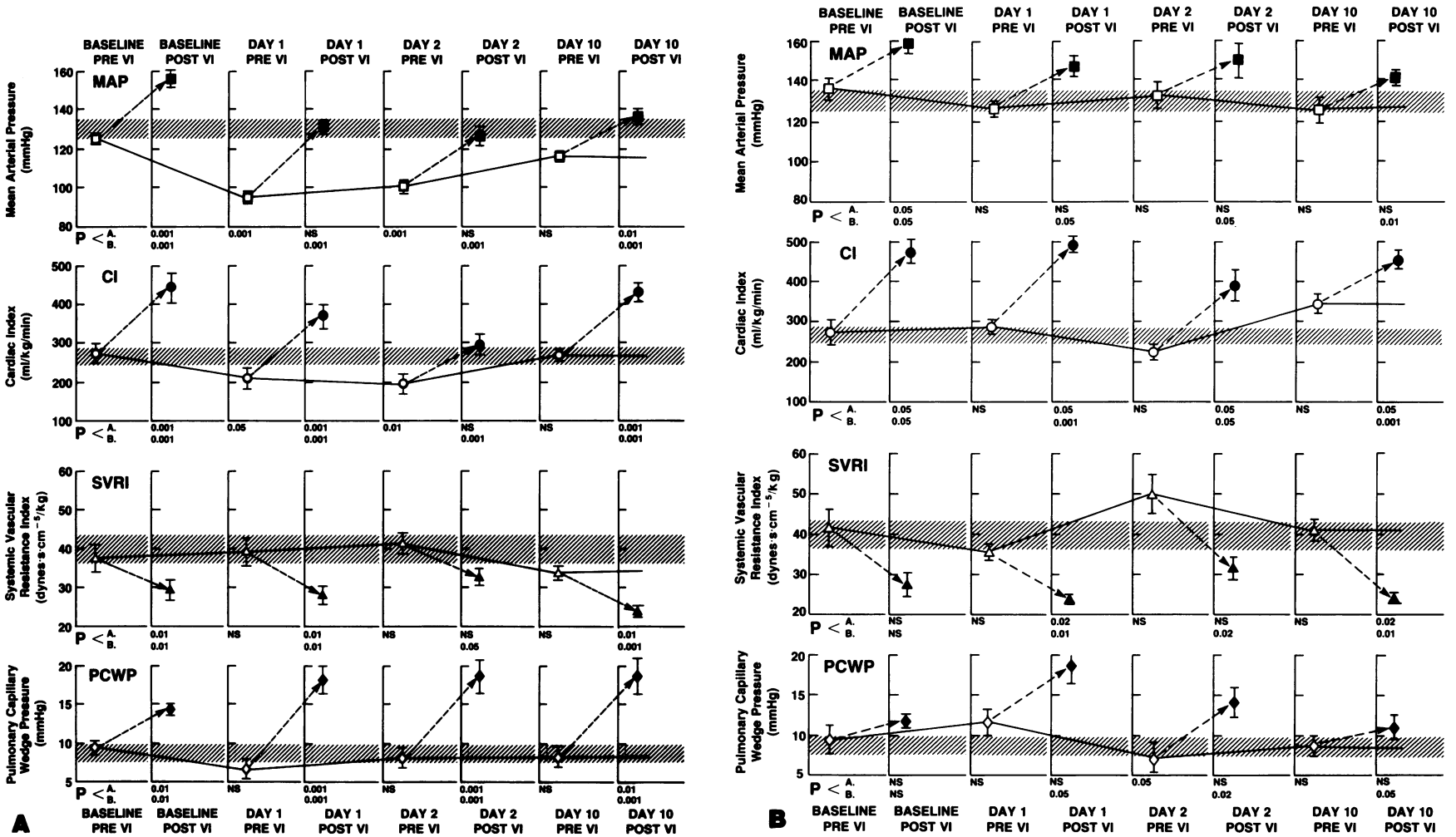


Figure 2. (*A*) Hemodynamic parameters of the 10 infected dogs; (*B*) hemodynamic parameters of the 6 control dogs (MAP, CI, SVRI, PCWP) as a function of time in days. The mean±SEM values for pre-VI are represented by the open geometric symbols and the post-VI values by the solid geometric symbols. The brackets represent the SEM. The solid lines connect the mean hemodynamic values pre-VI on serial days and the dotted arrows connect mean hemodynamic values for the pre- and post-VI each day. The cross-hatched areas represent the "normal" range and are the mean±SE values obtained from 51 other normal dogs standardized for comparison. The *P* values given in line A (indicated by lightface letter A) are obtained from paired-sample *t* tests for changes in each hemodynamic parameter from pre-VI baseline value to all subsequent values. The *P* values given in line B (indicated by lightface letter B) are obtained from paired-sample *t* tests of hemodynamic responses to volume infusion each day comparing pre-VI with post-VI values.

connected by a solid line. At each time point hemodynamics were measured before (open symbols) and after (closed symbols) aggressive VI. The before and after values are connected by a dashed arrow.

Fig. 2 *A* shows that at baseline, in the infected dogs, the means of each of the four hemodynamic parameters were close to or within the normal range for dogs, whereas after VI there was a statistically significant ($P < 0.01$) elevation of mean MAP, CI, PCWP, and a significant ($P < 0.01$) decrease in mean SVRI.

In infected dogs on day 1 of bacteremia, prior to VI, the mean MAP and CI decreased significantly compared to baseline from 124±3 to 95±3.5 mmHg ($P < 0.001$) and 275±22 to 209±24 ml/kg/min ($P < 0.05$), respectively. Mean PCWP and SVRI showed no significant change from baseline. On day 1, VI restored the mean (±SEM) MAP from 95±3.5 to 132±3 mmHg (i.e., no significant change from baseline pre-VI value of 124±3 mmHg). The VI has increased the bacteremia-induced depressed mean MAP back up to the "normal" range, but mean CI was significantly ($P < 0.01$) elevated to 366±27 ml/kg/min compared to the baseline pre-VI value of 275±22 ml/kg/min. In addition, on day 1, post-VI the mean SVRI had decreased significantly ($P < 0.01$) from pre-VI baseline value of 39.2±3.5 to 28.3±2.3 dynes · s · cm^{-5}/kg, respectively. Thus, on day 1, the post-VI hemodynamic profile was a hyperdynamic cardiovascular profile, i.e., a high CO and low SVRI.

To summarize, in bacteremic dogs, when preload is low, as evidenced by a low or normal mean PCWP prior to VI on day 1, the mean MAP and mean CI were decreased with a normal SVRI. Increasing preload restored the mean MAP to near normal, elevated mean CI, and a decreased mean SVRI. Thus, in this canine model the hyperdynamic profile of sepsis was preload-dependent.

In infected dogs on day 1 and 2 pre-VI, the systemic hemodynamics were not statistically different. On day 2, compared with day 1, VI increased CI to the normal range, but not supranormal levels. On day 2, compared with day 1, VI decreased SVRI to just below the normal range not statistically significantly decreased compared to the baseline pre-VI values. By day 10 (recovery), all four parameters had returned toward normal.

An overview of Fig. 2 *A* shows significant trends in hemodynamic values over time, both in terms of pre- and post-VI values. On days 1 and 2 both the MAP and the CI shifted down from the preoperative baseline values, and by day 10 these values returned toward baseline. In contrast, the SVRI (a ratio of the MAP and CI) showed very little serial change pre- and post-VI throughout. The PCWP showed no significant change pre-VI over serial time points, but at baseline post-VI the PCWP decreased compared to day 1, day 2, and recovery values.

In the control (nonseptic) dogs (Fig. 2 *B*), there was no significant mean change from baseline in any hemodynamic parameter at days 1 and 2, and recovery, other than a decreased PCWP ($P < 0.05$) on day 1 pre-VI. The responses to VI at all time points in the control group were similar to that at baseline.

Serial EFs. Serial EFs as determined by radionuclide scan (prior to VI) are shown in Fig. 3. The data for septic dogs are in Fig. 3 *A* and sterile clot dogs in Fig. 3 *B*. On the day of maximal change in EF, there was a highly significant ($P < 0.001$) decrease in mean EF compared with baseline in septic animals. There was no significant change in the EF in control dogs. EF decreased significantly ($P < 0.001$) in septic animals as compared with control animals. There was no difference between the recovery EF and initial EF in the septic or control group.

In 9 of 10 septic dogs the maximal decrease in EF occurred on day 2 and in one dog it occurred on day 3. Thus, septic animals developed profound decreases in EF during the 2–3 d after the onset of sepsis and recovered by 7–10 d. VI induced no significant changes (P = NS) in mean EF in each day in all canines (sterile and infected) animals.

Shifts in ventricular function. Employing a plot of EDVI vs. LVSWI, Fig. 4 depicts each individual dog's (*thin black arrows*) and the mean (*thick gray arrows*) shift in cardiovascular function after the peritonitis-induced bacteremia. From baseline to day 1 (*top panel*), all 10 bacteremic dogs showed a decrease in LVSWI and 8 of 10 dogs had a decrease in EDVI (Fig. 4). From day 1 to day 2 (*middle panel*), all 10 bacteremic dogs demonstrated an increase in EDVI with little or slight change in LVSWI. From day 2 to recovery (*bottom panel*), all 10 dogs had an increase in their LVSWI toward baseline, with inconsistent changes in EDVI.

Fig. 5 *A* and *B* depict another method of analyzing and displaying the serial time course changes in ventricular performance induced by peritonitis and bacteremia. The mean serial shifts in ventricular function are shown in bacteremic dogs in Fig. 5 *A*, and in sterile clot dogs in Fig. 5 *B*. The 95% confidence region is depicted by the ellipse surrounding the change each day in mean ventricular performance. Two statistical comparisons are used. First, hemodynamics are compared by analyzing sequential time points. Second, changes in the bacteremic group are compared with hemodynamic changes seen in control dogs.

Comparing baseline to day 1, the bacteremic dogs had both a 0.85±0.22 ml/kg mean decrease ($P < 0.01$) in EDVI and a 1.64±0.21 g-m/kg mean decrease ($P < 0.001$) in LVSWI. Then, from day 1 to day 2 the bacteremic dogs had a 1.48±0.3 ml/kg mean increase ($P < 0.001$) in EDVI, and an insignificant 0.16±0.13 g-m/kg mean increase in LVSWI. From day 2 to recovery, the bacteremic dogs had an insignificant 0.30±0.33 ml/kg mean decrease in EDVI and a 1.96±0.15 g-m/kg mean increase ($P < 0.001$) in LVSWI. In control dogs, no significant mean changes occurred from baseline to day 1, day 1 to day 2, or from day 2 to recovery (see Fig. 5 *B*).

Comparing the bacteremic and noninfected dogs from baseline to day 1, there was no significant difference in the change in EDVI but there was a more profound decrease ($P < 0.05$) in LVSWI in bacteremic dogs. From day 1 to day 2, there was a profound increase ($P < 0.01$) in EDVI in bacteremic dogs with no significant difference in the small day 1 LVSWI change, i.e., in only bacteremic dogs the ventricle dilated between days 1 and 2 with no significant change in the already depressed LVSWI.

From day 2 to recovery, there was no significant difference in the mean change in EDVI, but the bacteremic dogs had a large increase ($P < 0.01$) in mean LVSWI, showing a return of ventricular performance towards baseline.

In summary, bacteremic dogs had a significant mean decrease in EDVI and LVSWI on day 1. From day 1 to day 2 in the bacteremic dogs the ventricle dilated (increased EDVI) and maintained the same poor ventricular performance (decreased LVSWI). From day 2 to recovery, the mean ventricular performance improved in infected dogs and returned toward baseline. The sterile clot dogs had no significant shift in mean ventricular function throughout.

Ventricular function after VI. Fig. 6 displays the mean ventricular response to VI at baseline, day 1, day 2, and recovery. At baseline, VI greatly increased ($P < 0.01$) mean LVSWI and minimally increased (P = NS) mean EDVI. On day 1, day 2,

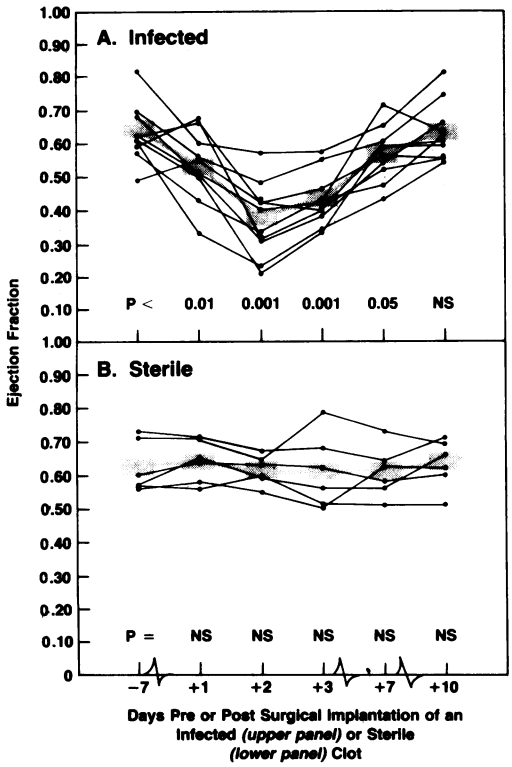


Figure 3. Individual serial dogs' EFs are shown by (●) in septic clot dogs (*A*) and sterile clot dogs (*B*) as a function of time in days. The lines connect individual dogs between days. The large gray bars are mean EF for all dogs on that day. *P* values are obtained from paired-sample *t* tests comparing serial time points to their respective baseline.

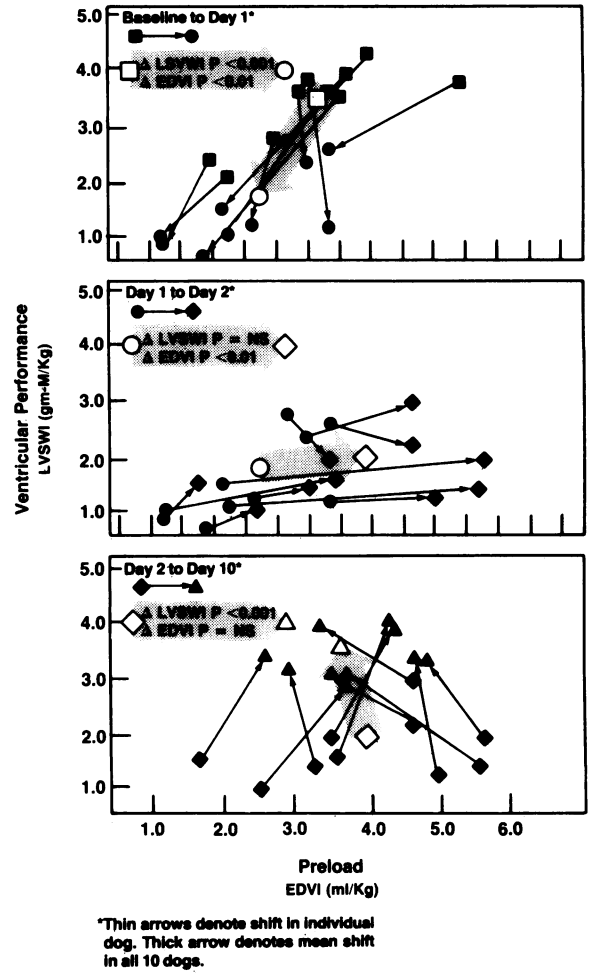


Figure 4. Shifts in ventricular function in individual bacteremic dogs are shown by thin black arrows on Starling plots of EDVI vs. LVSWI. Depicted on the top panel is baseline (■) to day 1 (●), on the middle pannel from day 1 (●) to day 2 (♦), and on the bottom panel day 2 (♦) to recovery (▲). On each respective panel the mean value for ventricular performance each day is represented by the same geometric figure (open) as the individual determination. The large gray arrows on each panel represent the mean shifts in ventricular function between days: *P* values (in upper left corner of each panel) are obtained from paired-sample *t* tests comparing the mean shift in ventricular function between days.

and recovery time points, the response to VI showed statistically significant increases ($P < 0.05$) in both mean EDVI and mean LVSWI.

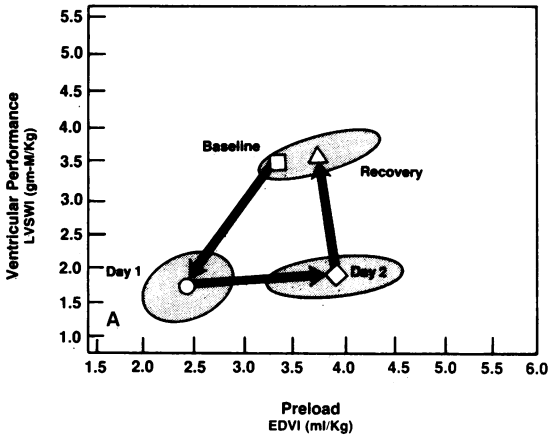
Fig. 6 shows that on day 1 VI reversed the bacteremia-induced depression of mean LVSWI to near baseline pre-VI (note the position of the arrow tip for day 1 value). The ability of volume to restore ventricular function to prebacteremia performance indicates that the defect on day 1 can be restored at least partially toward normal by increasing preload. On day 2 VI induced statistically significant ($P < 0.01$) ventricular dilatation, but the ventricular performance did not return to near baseline post-VI value (note position of arrow tip for day 2 value in Fig. 6). On day 2, ventricular performance was decreased, although mean ventricular volume 4.79 ml/kg was greater ($P < 0.01$) when compared to the pre- or post-VI values seen at baseline (see Fig. 6). This decrease in performance could result from decreased HR, increased afterload, or decreased intrinsic contractility. However, on day 2 post-VI, HR was greater than baseline ($P < 0.02$) and afterload, i.e., the MAP and SVRI, were not statistically elevated. Thus, the downward shift in the ventricular function curve appears to result from a decrease in the intrinsic contractility of the left ventricle.

By recovery, VI produces changes in ventricular function and ventricular size that were very similar to baseline values. The control dogs showed no significant shifts in ventricular performance or size pre- or post-VI throughout the study.

Analysis of the shifts in the relationship of EDVI and PCWP. Fig. 7 shows the relationship between the mean EDVI and the mean PCWP pre- and post-VI on serial days in infected dogs (Fig. 7 *A*) and sterile clot dogs (Fig. 7 *B*). The mean shift in the relationship between serial time points (baseline, day 1, day 2, and recovery) is derived from the midpoint values (see statistical methods) for EDVI and PCWP from the pre- to post-VI points for each dog on each day. The midpoint differences for each dog between days were determined and averaged, and these changes are compared to evaluate whether the changes occurred in the EDVI or PCWP or both.

In comparing the pre- and post-VI midpoint shift in EDVI and PCWP from baseline to day 1, the bacteremic dogs had a mean 0.14±0.11 ml/kg decrease (P = NS) in EDVI and a mean 0.6±1.26 mmHg increase (P = NS) in PCWP.

Between days 1 and 2, there was a substantial change in the volume/pressure relationship in diastole for the bacteremic dogs (note the midpoint shift Fig. 7 *A*). A profound 1.17±0.19 ml/kg increase ($P < 0.001$) occurred in EDVI, and there was a small 0.9±1.35 mmHg increase (P = NS) in PCWP.



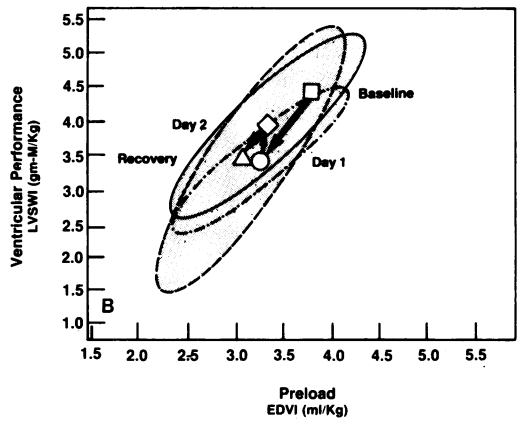


Figure 5. The serial mean shifts in ventricular function between days are depicted by the black arrows on Starling ventricular function plots of EDVI vs. LVSWI in infected clot dogs (*A*), and sterile clot dogs (*B*). The mean values each day for ventricular function are represented by baseline (□), day 1 (○), day 2 (◇), and recovery (△). In Fig. 4 the same open geometric figures and the same determinations of ventricular performance at serial time points are represented as in *A*. The gray ellipses around each large black arrow tip represent the 95% confidence regions for the shift in both the EDVI and LVSWI between days. In *B* the circles surrounding the confidence intervals for shift in ventricular performance between days are represented by: baseline to day 1 (-·-·-), day 1 to day 2 (——) day 2 to recovery (-----).

From day 2 to recovery, the bacteremic dogs had a mean decrease ($P < 0.05$) of 0.47±0.21 ml/kg in EDVI and an increase of (P = NS) 0.3±1.92 mmHg in PCWP. Thus, in the bacteremic dogs at recovery the EDVI was decreasing toward the baseline ventricular size.

In the sterile clot (control) dogs (Fig. 7 *B*), no significant changes occurred in EDVI or PCWP at any time points comparing day 1, day 2, and recovery with baseline values.

In summary, a comparison of baseline and serial time points in bacteremic dogs, demonstrated that the EDVI and PCWP were not significantly changed at day 1. At day 2 in bacteremic dogs, the EDVI was substantially increased without a change in pressure. This day 2 change suggests an increase in compliance, allowing an increase in ventricular volume without an increase in pressure.

Laboratory data. Tables III and IV show serial mean values for common clinical laboratory parameters obtained in bacteremic and control dogs, respectively. Table V shows the serial mean weights for the infected and control dogs. The weights provide further serial data that can be used to more fully evaluate serial volume status. The bacteremic dogs at day 1 had a metabolic acidosis (with full respiratory compensation) with a decrease in calculated bicarbonate to 19±1 meq/liter ($P < 0.001$) from a baseline of 21±0.3 meq/liter. However, arterial blood pH remained normal. On day 1, there was also a decrease in platelet counts from baseline value of 374±45 × 1,000/mm^3 to 189±21 × 1,000/mm^3 ($P < 0.01$). On day 2 the bacteremic dogs had the following abnormalities: metabolic acidosis compared to baseline value ($P < 0.01$) with the persistence of respiratory compensation noted on day 1; an elevated white blood count (21±2 × 1,000/mm^3 from a baseline of 11.8±1 × 1,000/mm^3 [$P < 0.02$]); decreased hematocrit (0.37±0.02 from a baseline of 0.46±0.03 [$P < 0.05$]); and a more pronounced thrombocytopenia (96±12 × 1,000/mm^3 from a baseline of 374±45 × 1,000/mm^3 [$P < 0.001$]). By day 10 the metabolic acidosis and the thrombocytopenia have resolved, but the anemia ($P < 0.01$), and the elevated white blood count ($P < 0.01$) have persisted.

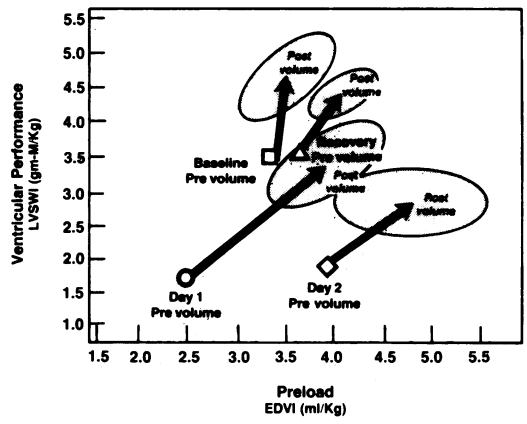


Figure 6. The mean shifts in ventricular performance in response to volume infusion are depicted by black arrows on Starling plots of EDVI vs. LVSWI. The geometric figures at the bases of the arrows represent the same pre-VI values of mean ventricular performance at serial time points—baseline (□), day 1 (○), day 2 (◇), recovery (△)—that were used in Figs. 4 and 5 *A*. The mean ventricular performances after VI are represented by the arrow tips at the respective serial time points. The gray ellipses represent 95% confidence regions for the post-VI values represented by the tips of the arrows.

On day 1 after surgery the sterile clot dogs also have a decreased bicarbonate of 17±1 meq/liter from a baseline 22±.5 meq/liter ($P < 0.05$) with respiratory compensation. At day 2 the sterile clot dogs' metabolic parameters are all within normal ranges. By day 10 the sterile clot dogs have a mild anemia and an elevated white blood count.

All hemodynamic studies were performed on dogs with normal serum pH and Po_2. No dog had a severe abnormality of blood chemistries (Na, K, CO_2, Cl, Glu, or Ca) that could have accounted for the decrease in cardiovascular function.

Discussion

This study demonstrates that significant reversible systolic myocardial depression and ventricular dilatation, as well as diastolic

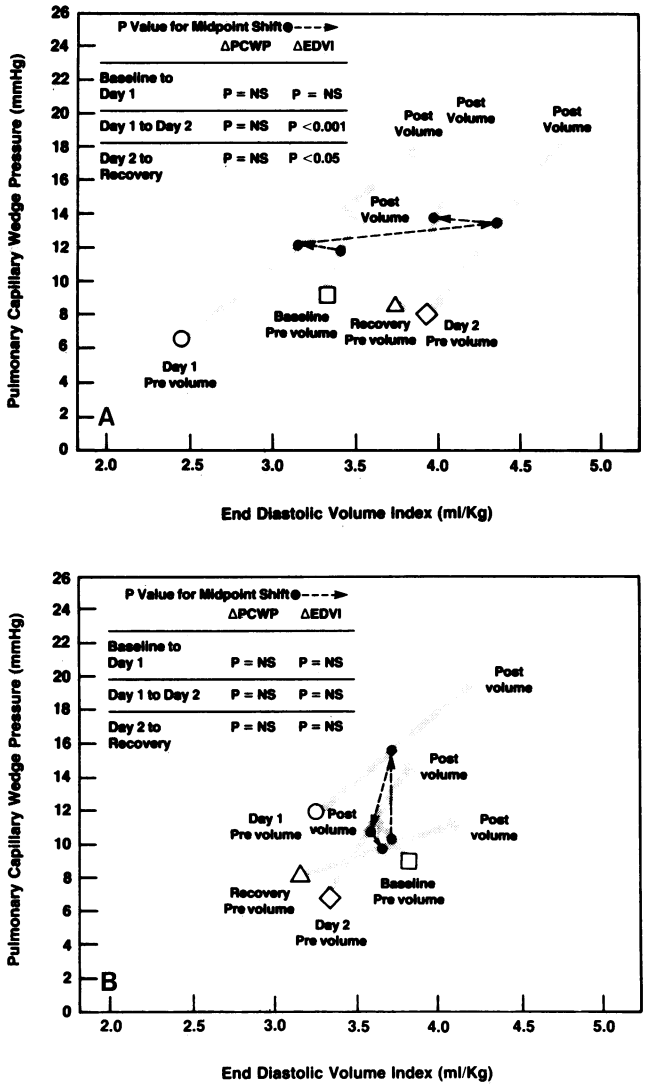


Figure 7. The mean shifts in ventricular volume/pressure relationships in response to VI are depicted by large gray arrows on compliance curve plots of EDVI vs. PCWP in infected clot dogs (*A*) and sterile clot dogs (*B*). The mean volume pressure relationships at pre-VI serial time points are represented as follows: baseline (□), day 1 (○), day 2 (◇), and recovery (△). The mean volume/pressure relationships after VI are represented by the arrow tips at the respective serial time points. The mean midpoint (see statistical methods) each day of the pre- and post-VI volume/pressure curve (*large gray arrows*) is represented by a small black dot. The shifts in the volume/pressure curves (midpoint) between days are represented by dashed black arrows. *P* values are obtained from paired-sample *t* tests comparing the midpoint shifts in PCWP and EDVI between days.

ventricular abnormalities, occur in a canine model of septic shock that simulates many of the features of the human form of this disease. The similarities between this canine model and human sepsis include the following: (*a*) live organisms (not endotoxin) are implanted in the peritoneum producing a nidus of infection (not direct intravenous injection) which then serves as a focus for dissemination into the bloodstream causing bacteremia, (*b*) hemodynamic and radionuclide determinations are performed serially over days (not a single time point evaluation), (*c*) dogs are evaluated without anesthesia or sedation, because these latter interventions are believed to affect cardiovascular function, (*d*) dogs are evaluated before and after a volume infusion.

In the clinical setting when sepsis is suspected or diagnosed, almost all patients are immediately treated with large fluid infusions; therefore septic patients are almost invariably evaluated after substantial fluid loading. Recent studies of humans who develop septic shock demonstrate that most patients have a hyperdynamic circulatory state with a high CO and low SVR (7–15).

In the present study, dogs demonstrate a hyperdynamic pattern only after receiving a substantial amount of volume. This observation suggests that the hyperdynamic hemodynamic profile characteristic of early septic shock is dependent, at least in part, on adequate preload (30, 31). Furthermore, early studies of human septic shock described a low CO (32); this finding may have resulted from lack of therapy with large VI in these earlier studies and thus resulted in a low CO owing to inadequate preload. In a previous study using a similar canine model of *E. coli* peritonitis, volume infusion was associated with a hyperdynamic circulatory pattern although pre-volume hemodynamics were not reported in these experiments. Further, the study employed pulmonary capillary wedge pressure as the measure of preload, so that sepsis-induced compliance changes may have accounted for some of the described changes (28).

Although CO is typically elevated in human septic shock, recent data demonstrate that there is a large subpopulation of patients with septic shock who develop a profound but reversible decrease in myocardial performance, characterized by a decrease in radionuclide-determined ejection fraction and dilatation of the left ventricle, with maintenance of this normal or high CO (16). Because these data were obtained in humans, optimal therapy with fluids, pressors, and other medications was mandatory. These interventions present potentially confounding variables, although it should be noted that a subpopulation of these septic shock patients had received only fluids, and this latter group demonstrated a similar decrease in EF and ventricular dilatation to the group of patients treated with fluids and pressors. The findings in the present canine study demonstrate that profound, reversible myocardial depression (decreased ejection fraction) and ventricular dilatation occur in the absence of therapy confirming that ventricular dysfunction results from the bacteremia, not the therapy. The findings in this dog model and human data are remarkably similar. The degree of depression in EF from normal to EFs of ~0.20 to 0.35 is similar to that seen in humans. The timing of the EF depression, occurring on days 1–4 and normalizing by day 10, is also similar in dogs and humans (16). It is of note that these cardiovascular findings in human sepsis (consisting of a reversible decrease in ejection fraction and significant ventricular dilatation) have been confirmed by an independent group of investigators (33).

The radionuclide-gated blood pool scan has been accepted as an excellent method to obtain left ventricular ejection fraction (34). In fact, because this radionuclide method does not employ the geometric assumptions necessary to calculate ejection fraction with the contrast-dye angiographic technique, many authors have argued that the radionuclide count method provides the most accurate determination of ejection fraction. Further, previous studies of coronary artery disease patients determined that the LV performance measured by EF is an independent prognostic factor predicting future survival, and resting cardiac index

Table III. Laboratory Values—Infected Clot Dogs

	pH	P_{CO_2}	P_{O_2}	HCO_3^-	Hct	WBC	Plat	Glu	Ca^{++}	BUN	Creat	Na^+	K^+	Cl^-
		torr	*torr*	*meq/liter*	*%*	*1,000/mm³*	*1,000/mm³*	*mg/dl*	*mg/dl*	*mg/dl*	*mg/dl*	*meq/liter*	*meq/liter*	*meq/liter*
Baseline														
Mean	7.35	39	96	21.2	44.3	13.6	374	89.6	9.3	13	0.91	151	4.7	115
SE	0.010	1.16	2.76	0.34	2.16	2.05	45.2	11.1	0.2	1.56	0.11	2.74	0.2	6.2
n	9	9	9	9	9	9	8	6	2	8	8	8	8	8
P<														
Day 1														
Mean	7.36	33	94.6	18.8	48.8	16.2	189	—	—	17.2	1.25	156	4.8	116
SE	0.007	1.02	3.89	0.68	2.45	1.44	21.5	—	—	4.89	0.14	3.73	0.2	3.3
n	6	6	6	6	10	10	10	—	—	4	4	4	4	4
P<		0.01		0.01			0.01							
Day 2														
Mean	7.32	30.4	99.6	16.6	37.4	21.2	95.8	74.5	8.1	9.77	0.75	145	3.7	113
SE	0.023	1.61	3.45	1.16	1.99	1.99	12.8	1.14	0.4	1.17	0.06	1.4	0.2	4.9
n	9	9	9	9	8	8	8	4	4	8	6	8	7	8
P<		0.001		0.05	0.05	0.02	0.001						0.05	
Recovery														
Mean	7.35	38.1	97.1	21	33.2	23.8	365	87.3	8.4	13.4	0.83	145	4.5	94
SE	0.01	1.15	3.12	0.42	1.16	1.32	30.5	7.39	0.5	1.54	0.06	1.3	0.1	9.1
n	10	10	10	10	8	5	7	6	6	10	10	10	8	10
P<					0.001	0.01								

Abbreviations: Hct, hematocrit; WBC, leukocytes; Plat, platelets; Glu, glucose; BUN, blood urea nitrogen; Creat, creatinine.
P values resulted from two-sample *t* tests comparing day 1, 2, or recovery to baseline value.

Table IV. Laboratory Values—Sterile Clot Dogs

	pH	P_{CO_2}	P_{O_2}	HCO_3^-	Hct	WBC	Plat	Glu	Ca^{++}	BUN	Creat	Na^+	K^+	Cl^-
		torr	*torr*	*meq/liter*	*%*	*1,000/mm³*	*1,000/mm³*	*mg/dl*	*mg/dl*	*mg/dl*	*mg/dl*	*meq/liter*	*meq/liter*	*meq/liter*
Baseline														
Mean	7.38	35.8	101	21.6	46.4	11.8	357	113	9.9	12.1	1.01	150	4.4	110
SE	0.02	2.43	2.1	0.45	2.6	1.15	41.1	8.83	0.2	1.29	0.07	1.91	0.0	0.7
n	6	6	6	6	4	4	4	2	2	6	6	6	6	6
P<														
Day 1														
Mean	7.4	27.7	94.2	17.2	44.1	28.7	257	—	—	10.5	1.05	146	4.2	111
SE	0.015	1.84	3.47	0.96	1.7	2.95	38.5	—	—	2.16	0.11	2.43	0.1	1.1
n	4	4	4	4	3	3	3	—	—	4	4	4	4	4
P<				0.05		0.001	0.01							
Day 2														
Mean	7.42	32.5	93.3	20.6	39.5	13.9	241	80.5	8.8	12.3	0.86	141	4.1	103
SE	0.02	2.5	9.89	0.76	1.59	1.16	69.2	3.18	0.1	1.67	0.06	1.83	0.1	3.1
n	6	6	6	6	2	2	2	2	2	6	5	6	6	6
P<														
Recovery														
Mean	7.41	33.8	97.2	21	34.7	22.3	457	—	—	10	1.1	138	4.8	109
SE	0.01	1.38	4.43	0.7	1.25	2.49	21.2	—	—	1.06	0.15	5.58	0.4	2.3
n	6	6	6	4	3	3	3	—	—	4	4	4	4	4
P<					0.001	0.001								

Abbreviations as in Table III.
P values resulted from two-sample *t* tests comparing day 1, 2, or recovery to baseline value.

Table V. Serial Mean Weights

	Baseline	Day 1	Day 2	Recovery
	kg	*kg*	*kg*	*kg*
Control dogs $n = 6$	12.37±37	12.50±0.77	12.25±0.64	12.52±0.68
Infected dogs $n = 10$	12.04±0.47	11.65±49*	11.36±0.45*	11.43±0.37‡

P values resulted from paired-sample *t* tests comparing means from days 1, 2 or recovery to baseline.
* $P < 0.01$.
‡ $P < 0.05$.

does not possess prognostic capability (35). The accuracy and prognostic capability of the ejection fraction led to its use to study septic shock. In addition, by performing radionuclide-gated blood pool scans and thermodilution cardiac outputs simultaneously, previous studies have shown that the EDVI can be easily calculated (36) (see Methods), providing an accurate measure of ventricular volume.

In addition to demonstrating decreased EFs and ventricular dilatation, the present study also employed ventricular function curves plotting a volume measure of preload (EDVI) vs. ventricular performance (LVSWI). It should be noted that the ventricular function curves employed in the present study used end-diastolic volume (not pressure) as the measure of preload. By using a measure of end-diastolic volume as preload, this study avoids the problem of confusing changes of ventricular compliance with changes in performance, a common problem when pressure is used as the measure of preload (37). By plotting serial changes in ventricular function at serial time points for individual dogs or for the average of all the septic dogs, ventricular dysfunction was demonstrated on days 1 and 2 after bacteremia (see Figs. 4 and 5).

Another method of evaluating ventricular performance employed in this study was to evaluate the response to VI. A two-point ventricular function curve was constructed on each dog at every time point by plotting the pre- and post-VI response in ventricular volume and performance. The day 1 decrease in ventricular performance could be brought back to near baseline with VI, i.e., the decrease was preload-dependent (see Fig. 6). However, VI at day 2 after bacteremia failed to increase ventricular performance back to baseline levels despite increasing preload (as measured by pressure [PCWP] or volume, [EDVI] parameters) to supranormal levels. The ventricular dysfunction on day 2 after bacteremia probably results from a decrease in the intrinsic contractility of the left ventricle.

Thus, in this canine model, bacteremia induces both a preload-dependent (day 1) and a preload-independent (day 2) decrease in ventricular performance. The pathogenesis of this systolic ventricular dysfunction is not known. Recent studies in human septic shock have demonstrated that coronary blood flow is not a likely etiology (38). However, other recently completed investigations present strong evidence that a circulating myocardial depressant substance is probably the cause of the decreased EF in human septic shock (39). The role of other recently described circulating substances in the pathogenesis of septic shock will require further investigations.

Previous studies of animals or humans did not describe the myocardial depression so clearly evidenced in the present study because many prior investigations only evaluated myocardial function for several hours after the onset of sepsis (40, 41) (most canine endotoxin models caused death of the animal in 3–6 h). Other previous investigations failed to discover the severe myocardial dysfunction seen in this study because they employed only cardiac output as the measure of cardiovascular performance (8–10). By employing simultaneous determinations of thermodilution cardiac output and radionuclide scan-determined EF, the present study employed sophisticated cardiovascular monitoring to serially evaluate the cardiac response to Gram-negative sepsis. Cardiovascular evaluation employing only conventional intravascular catheter-derived hemodynamics would have missed the depressed EF and dilated ventricle demonstrated by simultaneous determination with both conventional hemodynamics and nuclear scan. Employing similar simultaneous studies, previous investigations demonstrated similar cardiovascular dysfunction in humans with septic shock (16, 33, 42). To summarize, in the present study three methods of evaluating systolic ventricular dysfunction (serial scan determined EFs; shifts in ventricular function curves, EDVI vs. LVSWI; and the response of ventricular performance to VI) documented severe, reversible decreases in systolic ventricular function induced by bacteremia.

During diastole, one of the important properties of the ventricle is the compliance or "stiffness" of the ventricular myocardium. Recent studies of cardiovascular function have elucidated important abnormalities of diastolic ventricular function in ischemic and other structural heart disease (43, 44). Although this property has been defined in slightly different ways by different authors, all agree that it represents the relationship between ventricular volume and ventricular pressure. Since this relationship is neither linear nor clearly exponential, most authors have not employed a purely mathematical model of the volume/pressure relationship, but rather have demonstrated shifts in the volume/pressure curve with physiologic interventions (45–49).

In the present study, thermodilution cardiac outputs and radionuclide-gated blood pool scans were performed simultaneously (both within 2–3 min) allowing calculation of ventricular volumes (see above in Methods) at the same time that ventricular pressures and cardiac outputs (flows) were being measured. Then, each dog at each time point received an identical rapid fluid infusion and the studies were repeated. This allowed determination of the volume/pressure relationship, both before and after the ventricle was distended by the administration of fluid (Fig. 7). Bacteremia produced significant changes in diastolic ventricular function. This diastolic abnormality was characterized by a significant increase in volume in relationship to pressure when compared to normal ventricles at baseline. The maximal diastolic abnormality was seen on day 2 when there was massive LV dilatation without a significant change in pressure. Whether this diastolic abnormality is a direct consequence of bacteremia, or represents a compensatory mechanism of the ventricle to allow a larger diastolic volume without a pressure increase that would produce pulmonary edema, is not known. No previous study has demonstrated a change in the diastolic ventricular volume/pressure relationship due to sepsis, although increases and decreases in ventricular compliance have been described at different times after acute myocardial ischemia (43). Elucidation of the cause of this ventricular diastolic abnormality will require further investigation.

Recently, Ziegler et al. (6) employed insights regarding the pathogenesis of sepsis to devise improved therapy. This study describes profound systolic and diastolic abnormalities that are potential sites for an improved therapeutic regimen in this highly lethal disease.

Acknowledgments

The authors thank Robert L. Danner, M.D., Kevin W. Peart, Gary L. Akin, Mike E. Flynn, John Stewart, John K. Warrenfeltz, Nelson L. Flemming, Jim Foster, Ernie Corral, Robert J. Bain, Dean Caneal, and David W. Reusch for their technical support during the study; Major James E. Hall, Major Jerome Sauber, Major James Rogers, Captain Gordon Rahmus for veterinary care and surgical procedures; David W. Alling for statistical analysis; and, for preparation of the manuscript, Sue Oremland and Sue LaRoche.

Research Task Nos. MR000.00-1287 and 4441-00082.

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