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Effect of Continuous Arteriovenous Hemofiltration Combined with Systemic Vasopressor Therapy on Depressed Left Ventricular Contractility and Tissue Oxygen Delivery in Canine Escherichia coli *Sepsis*

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Background: **In a previous study, we showed that continuous arteriovenous hemofiltration (CAVH) reversed the depression in left ventricular (LV) contractility in canine *Escherichia coli* sepsis by the removal of a circulating substance the molecular weight of which is less than 30,000. Despite the normalization of LV contractility, however, we were unable to demonstrate an improvement in systemic arterial blood pressure (BP), presumably because the mechanisms underlying the depression in LV contractility and the decrease in BP are different in sepsis. In the current study, we examined the effect of combined treatment with CAVH and the α-adrenergic agonist phenylephrine on LV mechanics and tissue oxygen delivery in our canine *E. coli* model.**

Methods: **Measurements were obtained at baseline (condition B), after 4 h of sepsis (condition S), and after 2 h of CAVH and phenylephrine (condition P) (total of 6 h of sepsis). During P, phenylephrine was infused to restore BP to that found at baseline. The slope of the end-systolic pressure–dimension relation was used as the index of LV contractility; LV anterior–posterior dimensions were measured by sonomicrometry.**

Results: **During combined CAVH and phenylephrine treatment, the decrease in the slope of the end-systolic pressure–dimension relation otherwise observed at S was reversed. The slope (mean ± SD) was 57.5 ± 32 mmHg/mm at B *versus* 22.2 ± 8 mmHg/mm at S ($P < 0.05$, B *vs.* S) *versus* 62 ± 37 mmHg at P ($P < 0.05$ S *vs.* P) (analysis of variance). Mean BP was restored to that found at B (123 ± 19 mmHg *versus* 82 ± 14 mmHg ($P < 0.05$ B *vs.* S) *versus* 116 ± 27 mmHg ($P < 0.05$ S *vs.* P). Combination treatment with CAVH and phenylephrine also improved stroke volume (39.3 ± 13.5 *versus* 32 ± 8 *versus* 44 ± 12 ml) and tissue oxygen delivery during P compared with results obtained when phenylephrine was given alone.**

Conclusions: **Our study offers a rationale for the combined use of phenylephrine and CAVH in the reversal of cardiac depression and hypotension in sepsis. (Key words: Blood pressure: hypotension. Heart: myocardial depressant factor. Heart, myocardial depression: continuous arteriovenous hemofiltration treatment. Shock: endotoxin. Sympathetic nervous system, catecholamines: phenylephrine.)**

IN humans with sepsis and in experimental models of sepsis, a depression in left ventricular (LV) contractility that recovers during convalescence has been demonstrated.[1] Although the mechanism underlying this reversible loss of myocardial systolic function remains unclear, several investigators have related this depression to a circulating filterable cardiodepressant substance (FCS) of relatively low molecular weight (<30,000).[2,3]

In a previous study, we were able to show that removal of such a factor or factors from the circulation of intact animals by continuous arteriovenous hemofiltration was associated with recovery of LV contractility in a canine model of *Escherichia coli* sepsis.[4] However, despite this recovery of LV contractility after hemofiltration in our experimental model, we were unable to demonstrate a significant improvement in systemic arterial pressure. We concluded that the most likely explanation for this finding was that in sepsis, the mechanisms responsible for myocardial depression and those that produced hypotension, presumably by arterial vasodilation, were different.[4]

Although vasopressor agents can be used to counteract arterial hypotension in sepsis, one concern with this approach is that vasoconstricting agents increase

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impedance to LV ejection and might thereby reduce stroke volume (SV) and oxygen delivery to the tissues. This reduction in SV would be particularly magnified in sepsis because of the substantial decrease in contractility, as observed in our previous study.[4]

In our previous study,[4] LV contractility was defined in terms of the LV end-systolic pressure–dimension relation (LVESPDR).[5,6] This index is relatively independent of LV preload or afterload and is defined by the linear equation $P_{es} = E_{es} (D_{es} - D_0)$, where E_{es} = the slope of the relation and defines contractility; P_{es} and D_{es} = end-systolic pressure and end-systolic dimension, respectively; and D_0 = the extrapolated dimensional intercept to zero end-systolic pressure. We previously found that during sepsis, E_{es} decreases to less than one half that found presepsis.[4] According to the above equation, if a vasoconstricting agent were used during sepsis to restore systemic arterial blood pressure (BP) and thereby increase P_{es} to a normal level, the increase in D_{es} would be about twice that found in the normal state. It follows that if LV end-diastolic dimensions (LVEDD) were unchanged between normal and septic conditions, a greater increase in D_{es} would result in a larger reduction in SV and therefore a larger reduction in tissue oxygen delivery in sepsis (*i.e.,* SV is proportional to LVEDD $- D_{es}$).

We reasoned, however, that a vasoconstrictor-mediated increase in systemic BP in sepsis might have less negative influence on SV and cardiac output (CO) if myocardial contractility were first restored to near normal by hemofiltration. In the current study, we used our canine model of *E. coli* septicemia to test this hypothesis. If, as hypothesized, combined treatment with hemofiltration and the α-adrenergic vasoconstrictor phenylephrine[7] results in lesser reduction in SV than when phenylephrine alone is used to restore BP in sepsis, this finding would provide support for further exploration of the potential of the combined use of hemofiltration and vasoconstricting agents in the treatment of impaired contractility and systemic hypotension, respectively, in human subjects with sepsis.

Materials and Methods

Sepsis Model and Study Design

These studies were performed in accordance with protocols approved by the university Animal Care Committee. Canine sepsis was induced as previously described by intravenous infusion of 10^{10} colony-forming units of live *E. coli* (serotype 0111:B4) given over a 30-min interval.[4] A constant infusion of approximately 5×10^9 colony-forming units/h of *E. coli* was maintained over the remainder of the experiment to give a total of 6 h of bacteremia. Measurements were obtained before sepsis (baseline) and repeated after 4 h of sepsis when depression LV contractility was observed in our previous study.[4] After the 4-h measurement, each animal was randomly assigned to one of the four groups in which different treatments were administered over the next 2-h period. In group 1, no treatment was given, and this group served as a time control group. In group 2 hemofiltration alone was used over this interval, because the results obtained in our previous study indicated that 2 h of hemofiltration were necessary to restore contractility to baseline in our model.[4] In group 3 phenylephrine alone was infused over this 2-h interval; the dose given was that which was required to restore mean BP to approximately baseline values. In group 4, continuous arteriovenous hemofiltration was combined with phenylephrine treatment, also administered continuously over this 2-h interval.

The animals were randomly assigned to one of the four groups, and each group consisted of ten mongrel dogs (20–30 kg). In the respective groups, LV filling pressures were maintained the same during the three conditions (*i.e.,* at baseline, 4 h, and 6 h) and averaged approximately 10 mmHg. Six percent hetastarch in normal saline solution was used as a volume expander and was given intravenously as required to maintain appropriate filling pressures in the three conditions.

In the current study, no nonseptic control groups were included. No control group was believed necessary because in our previous study in which the effects of hemofiltration and hypotension *per se* on cardiac mechanics were examined in nonseptic dogs, no changes in parameters were observed over a 6-h period.[4] However, it was thought necessary to include a sham hemofiltration group because hemofiltration for a 2-h period could unload the LV and in this way improve LV function without necessitating that a circulating FCS had been removed. In seven animals, therefore, measurements were obtained at baseline, 4 h postsepsis, and 6 h postsepsis, but during the 4- to 6-h period, although the animal was connected to the extracorporeal circuit, hemofiltration was not performed (see discussion of sham hemofiltration group in Results).

Animal Preparation and Hemodynamic Measurements

Healthy mongrel dogs were brought to the laboratory, anesthetized with sodium pentobarbital (30 mg/kg). The trachea was intubated, and the lungs were mechanically ventilated (Harvard Apparatus, South Natick, MA). The ventilator settings were adjusted to maintain arterial P_{CO_2} at about 35 mmHg and *p*H at 7.35. In the four groups, respiratory rate was varied as necessary to maintain *p*H in the normal range between conditions (see Discussion). During the course of the experiment, the inspired oxygen concentration was also varied as necessary to maintain hemoglobin oxygen saturation approximately 100%.

In addition, supplemental pentobarbital was administered during the study according to the following protocol to maintain relatively constant plasma concentrations throughout the experiment.[4,8,9] Based on the kinetics of pentobarbital elimination, the half life of pentobarbital is approximately 8 h.[8] Because the experiment lasted for approximately 8 h, the additional dose of pentobarbital would consist of one half the initial anesthetizing dose. The latter dose was administered over the time course of the experiment and was given in three equally divided doses approximately every 2.5 h from the initiation of the experiment. As previously described,[4] these additional doses were slowly infused intravenously (over a 10–15–min period) and were administered at least 45 min before measurements were made in a given condition to ensure relatively stable concentrations.

Vascular catheters were inserted under sterile conditions. An arterial catheter was placed in the left femoral artery for the acquisition of blood to monitor arterial blood gases and for continuous recording of mean arterial pressure. Another catheter was placed into one jugular vein for the infusion of fluids and supplemental anesthesia as required. Into the other jugular vein, a thermistor-tipped catheter was advanced into the pulmonary artery to measure mean pulmonary arterial pressure, pulmonary wedge pressure, right atrial pressure, and CO by the thermodilution technique (Columbus Instruments, Columbus, OH). All of the fluid-filled catheters used for vascular pressure measurements were connected to transducers (Statham, Hato Rey, Puerto Rico) and were referenced to the level of the left atrium. Measurements were obtained with the animal placed in the supine position and were taken at end-expiration, during which the ventilator was turned off for approximately 3–5 s. All signals were displayed on an eight-channel recorder (Hewlett-Packard, Palo Alto, CA).

In groups 2 and 4, the right femoral artery and vein were additionally cannulated with polyethylene catheters for connection to a hemofilter (CAVH Kit FH66, Gambro, Hechingen, Germany).[4] The hemofilter permits all solutes up to a molecular weight of approximately 30,000 to be removed from the plasma. In groups 2 and 4, 1.5–2 l filtrate was removed from the blood over the 4- to 6-h interval. During hemofiltration an arterial–venous flow rate of 2–3 l/min through the hemofilter was maintained with a roller pump (Cobe Perfusion System, Lakework, CO), and the fluid removed was replaced with Ringer's solution given intravenously to maintain a constant circulating blood volume and to keep the arterial *p*H between 7.28 and 7.38. In all groups, the blood of each animal was anticoagulated (3 ml:1,000 i.u./ml) immediately after the 4-h measurement.

In the four treatment groups, each full set of hemodynamic measurements obtained at each study condition consisted of arterial blood gas measurements and central hemodynamics. The latter included right atrial pressure, pulmonary arterial pressure, BP, SV, systemic vascular resistance [SVR] and pulmonary vascular resistance [PVR]). Calculated values included SV (SV = CO/heart rate), SVR [SVR = (BP − right atrial pressure)/CO], and PVR [PVR = (pulmonary arterial pressure − pulmonary wedge pressure)/CO]. When parameters were obtained at each of the measurement intervals, so as not to interfere with the determination of CO or the other hemodynamic parameters, intravenous fluids were transiently discontinued, and in groups 2 and 4 at the 6-h point, the hemofiltration circuit was turned off.

Each full set of blood gas parameters obtained at each study condition included arterial and mixed venous blood samples, which were analyzed for oxygen and carbon dioxide tensions (P_{O_2} and P_{CO_2}) and *p*H with a blood gas analyzer (165–2, Corning Glass, Medfield, MA). Arterial and mixed venous oxygen contents were measured by means of carbon monoxide displacement technique and hematocrit.[10] Oxygen delivery was calculated as CO × arterial oxygen content (milliliters oxygen per minute).

Measurements of Cardiac Mechanics

Of the ten dogs studied in each group, measurements of cardiac mechanics were determined in five dogs. In these experiments, left ventricular end-systolic dimen-

sion (LVESD) and LVEDD were measured by sonomicrometry.[4,11,12] During the preparation, the sternum and pericardium were widely opened. The lungs were ventilated (as described above); 5 cmH_2O end-expiratory pressure (positive end-expiratory pressure) was applied to the airway. A pair of ultrasonic crystal transducers was placed subendocardially along the anterior–posterior minor axis of the LV to measure LVEDD and LVESD. Our previous study indicated that changes in dimensions measured along the anterior–posterior axis in our sepsis model were representative of those found along the septal–lateral and apex–base dimensions.[4] The ultrasonic crystal transducer method of measuring ventricular dimensions has been detailed elsewhere.[11,12] The wires from the crystal pairs were attached to a sonomicrometer (Sonomicrometer 120, Triton Technology, San Diego, CA), and the outputs were also displayed on the eight-channel recorder.

From a carotid artery incision, a high-fidelity transducer-tipped catheter (Millar Instruments, Houston, TX) was advanced into the LV for measurement of LV end-diastolic pressure and LV end-systolic pressure (LVESP). From the LV pressure tracing, LV end-diastolic pressure was defined as the pressure measured just before the sustained and rapid increase in LV isovolumic pressure.[12] In turn, LVEDD was defined by LV end-diastolic pressure. LVESP and LVESD were taken as the point in the cardiac cycle where pressure/dimension was at a maximum.[5] In addition, a 4-ml Fogarty catheter was inserted into the left femoral vein and positioned in the inferior vena cava such that venous return was maximally reduced when the balloon was inflated. This technique allowed multiple end-systolic pressure–dimension coordinates to be obtained in the generation of the LVESPDR, the slope (E_{es}) of which was used as our index of contractility.[5,6,11]

Changes in contractility between conditions were assessed by E_{es}. In terms defined by Sagawa,[5] end-systole is the point in the cardiac cycle at which the ratio of ventricular pressure to dimension reaches it highest value (maximal elastance). From the maximal pressure–dimension coordinates examined over multiple beats of different dimensions and pressures, a linear relation can be obtained, as described above. E_{es} defines contractility. The extrapolated dimensional intercept is not changed by the contractile state of the heart but may be influenced by changes in the resistance and capacitance properties of the peripheral circulation.[13]

Sagawa[5] and Sagawa *et al.*[6] have indicated that at least three pressure–dimension coordinates are necessary to construct LVESPDR. Accordingly, this was the minimum number measured during each condition. The balloon of the Fogarty catheter, positioned in the inferior vena cava, was rapidly inflated with normal saline. This inflation produced a transient venous occlusion with a progressive decrease in LVESD and LVESP. Venous occlusion was performed during end-expiration and took about 4 s. Linear regression analysis of the end-systolic pressure–dimension coordinates generated was then used to determine E_{es}. Although we used linear rather than volume dimensions to determine E_{es}, Little *et al.*[14] have shown that pressure–dimension and pressure–volume relations show similar changes in response to global alterations in ventricular contractility. Furthermore, because the end-systolic relation may be slightly curvilinear at the extremes of ventricular pressure, LVESDs were compared over a similar range of LVESPs during the respective conditions.[15]

In the five dogs in each group in which cardiac mechanics were determined, measurements of LVEDD, LVESD, LVESP, and E_{es} were obtained in addition to hemodynamic measurements during each of the three conditions.

Statistical Methods

Statistics included analysis of variance (ANOVA) for repeated measures for comparisons within a single group (ANOVA1R, NWA Statpak, Portland, OR). For between-group comparisons, the respective changes between the 4- and 6-h measurements in the four groups were analyzed by a one-way between-group ANOVA (ANOVA1, NWA Statpak). Furthermore, to check for differences in the baseline and 4-h measurements, we used a two-way ANOVA (*i.e.*, split plot design ANOVA2R1, NWA Statpak). A Student-Newman-Keul multiple range comparison test was used to determine differences when multiple measurements were compared. Results are reported as mean ± SD.

Results

In all four groups, mean BP measured at 4 h postsepsis decreased to approximately two thirds of that at baseline (fig. 1). In group 1 (time control group) and in group 2 (hemofiltration alone), no treatment for hypotension was instituted and BP remained unchanged between 4 and 6 h. In groups 3 and 4, phenylephrine infusion was begun at 4 h and was continued to 6 h, and by design mean BP measured at the 6 h measure-

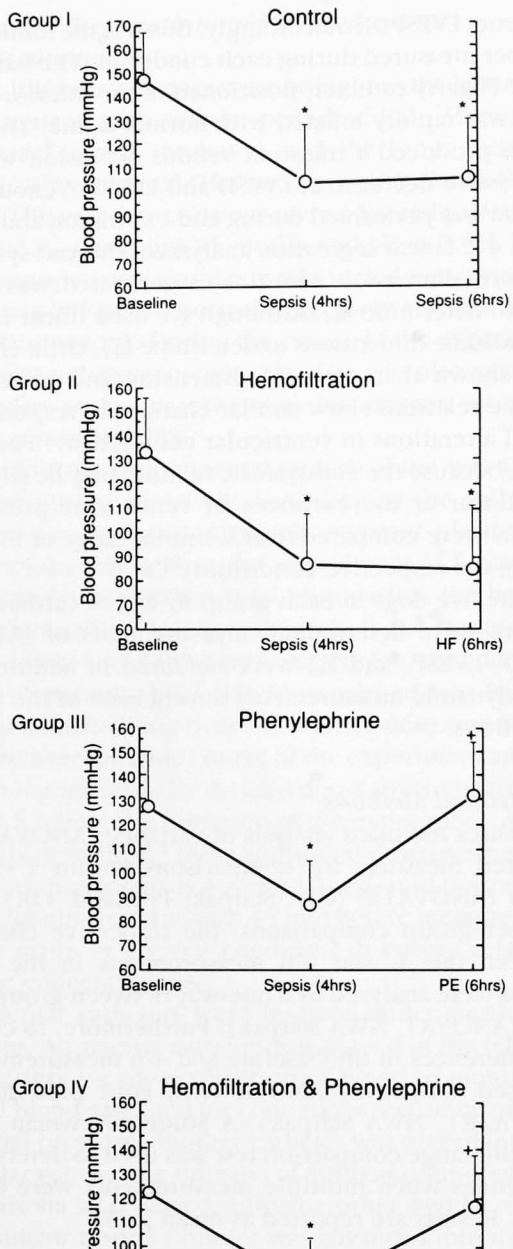


Fig. 1. Mean (±SD; n = 10) blood pressures in the four groups at baseline, 4 h postsepsis, and 6 h postsepsis. HF = hemofiltration; PE = phenylephrine. *$P < 0.05$ *versus* baseline within a group by repeated-measures analysis of variance and Student-Newman-Keul analysis; +$P < 0.05$ *versus* groups 1 and 2 in which the respective changes in blood pressure observed between 4 and 6 h postsepsis in the four groups are compared by one-way between-groups analysis of variance and Student-Newman-Keul analysis.

ment was similar to that at baseline. In groups 3 and 4, the dose of phenylephrine used varied widely between dogs. The mean doses used were not different between groups 3 and 4, and averaged 0.25 ± 0.17 mg/min and 0.34 ± 0.26 mg/min respectively.

Other hemodynamic measurements are shown in table 1. LV filling pressures (pulmonary wedge pressure) were not different between groups by two-way ANOVA ($P \approx 0.30$) and in the respective groups were unchanged between conditions. The other hemodynamic parameters obtained at the baseline and 4-h point were also not different between groups. In addition, LV filling dimensions as measured by LVEDD (table 2) were unchanged between conditions and were not different between groups.

SV measured in the four treatment groups are shown in figure 2. In group 1 (control group), SV was unchanged during the three conditions. In group 2, hemofiltration was performed between the 4-h and 6-h measurements, and SV obtained at 6 h postsepsis was significantly higher than that at 4 h postsepsis. In contrast, in group 3, phenylephrine alone was infused between 4 and 6 h, and SV measured at the 6 h was significantly less than that at 4 h postsepsis. In group 4, combined treatment with phenylephrine and hemofiltration was instituted. This treatment resulted in a significant increase in SV between the 4-h and 6-h measurements compared with the changes observed in groups 1 and 3. Changes in CO between conditions in the four groups paralleled those observed in SV and are shown in figure 3.

In the sham hemofiltration group (table 3), there were no increases in CO and SV in the 4- to 6-h interval, and during this interval, the hemodynamic findings were very similar to those found in group 1.

In groups 1–4, LVESPDR were used to assess changes in LV contractility during the course of the experiment. An example obtained in one dog in group 4 is shown in figure 4. At 4 h postsepsis, E_{es} was shifted downward and to the right compared with that obtained at baseline. Combined treatment with hemofiltration and phenylephrine reversed the reduction in E_{es} and restored it to that found at baseline.

In figure 5, E_{es} obtained at the baseline and 4 h conditions was not different between groups. In group 1, mean E_{es} progressively decreased over the 6-h period of sepsis; after 6 h of sepsis, E_{es} was less than half that found at baseline. In group 2 (hemofiltration alone), E_{es} at 4 h postsepsis was approximately one-half that found at baseline; hemofiltration reversed this depres-

Table 1. Hemodynamics in the Four Groups (n = 10)

	Group 1			Group 2			Group 3			Group 4		
	B	4 h	6 h	B	4 h	6 h	B	4 h	6 h	B	4 h	6 h
Pap (mmHg)	18 ± 4	17 ± 5	17 ± 4§	17 ± 5	19 ± 4	21 ± 6	15 ± 2	16 ± 4	16 ± 4§	19 ± 4	20 ± 4	23 ± 7
Pwp (mmHg)	10 ± 2	11 ± 2	11 ± 3	11 ± 3	11 ± 3	11 ± 3	9 ± 3	10 ± 4	10 ± 4	11 ± 3	11 ± 3	11 ± 5
HR (beats/min)	147 ± 29	124 ± 18	124 ± 22	138 ± 24	132 ± 16	116 ± 19*	129 ± 20	130 ± 28	110 ± 24	131 ± 12	134 ± 25	120 ± 19*
Rap (mmHg)	5 ± 2	6 ± 2	6 ± 2	6 ± 3	7 ± 3	7 ± 3	5 ± 1	5 ± 3	5 ± 3	6 ± 2	6 ± 3	6 ± 4
PVR (mmHg · L⁻¹ · min)	13 ± 4	12 ± 4	12 ± 4	12 ± 3	13 ± 3	14 ± 4	11 ± 3	12 ± 5	13 ± 5	13 ± 3	14 ± 3	17 ± 6

Table 1. Hemodynamics in the Four Groups (n = 10)

	Group 1			Group 2			Group 3			Group 4		
	B	4 h	6 h	B	4 h	6 h	B	4 h	6 h	B	4 h	6 h
Pap (mmHg)	18 ± 4	17 ± 5	17 ± 4§	17 ± 5	19 ± 4	21 ± 6	15 ± 2	16 ± 4	16 ± 4§	19 ± 4	20 ± 4	23 ± 7
Pwp (mmHg)	10 ± 2	11 ± 2	11 ± 2	9 ± 2	10 ± 2	11 ± 3	9 ± 3	9 ± 3	10 ± 4	11 ± 3	11 ± 3	11 ± 5
HR (beats/min)	147 ± 29	124 ± 18	124 ± 22	138 ± 24	132 ± 16	116 ± 19*	129 ± 20	130 ± 28	110 ± 24	131 ± 12	134 ± 25	120 ± 19*
Rap (mmHg)	5 ± 2	6 ± 2	6 ± 2	6 ± 3	7 ± 3	7 ± 3	5 ± 1	5 ± 3	5 ± 3	6 ± 2	6 ± 3	6 ± 4
PVR (mmHg·L^{-1}·min^{-1})	1.2 ± 0.4	1.0 ± 0.6	1.4 ± 0.7	1.6 ± 0.6	1.7 ± 1.0	1.9 ± 1.6	1.4 ± 0.7	1.3 ± 0.5	2.7 ± 2.0	1.9 ± 0.7	2.2 ± 1.0	2.0 ± 1.1
SVR (mmHg·L^{-1}·min^{-1})	28 ± 15	18 ± 8	21 ± 9	27 ± 9	16 ± 5*	15 ± 6*	27 ± 6	17 ± 8	64 ± 50†‡	25 ± 9	20 ± 11	22 ± 7

Values are mean ± SD.

B = baseline; 4 h and 6 h = 4 and 6 h post-sepsis, respective; Pap, Pwp, and Rap = mean pulmonary artery, capillary wedge, and right atrial pressures, respectively; HR = heart rate; SVR and PVR = systemic and pulmonary vascular resistances, respectively.

* $P < 0.05$ *versus* baseline and †$P < 0.05$ *versus* baseline and 4 h within a group by within group ANOVA and SNK.

‡ $P < 0.05$ between 4 and 6 h post-sepsis *versus* other groups by between groups ANOVA and SNK.

§ $P < 0.05$ change between 4 and 6 h in groups 1 and 3 *versus* group 4.

sion and returned E_{es} to the value found at baseline. In group 4, the treatment combination of hemofiltration and phenylephrine caused a reversal of the depression in E_{es} found at 4 h postsepsis in a manner similar to what was observed in group 2. In group 3, phenylephrine alone was given, and mean E_{es} did not change between 4 and 6 h postsepsis. In all groups, the mean correlation coefficients for the calculations of LVESPDR were equal to or greater than 0.9 in all conditions (range 0.91–0.99). Moreover, in the five experiments in each group in which cardiac mechanics were determined, hemodynamic measurements were not different from those determined in the other dogs.

Measurements of LVESP and LVESD are shown in table 2. In group 1, LVESP measured at 4 and 6 h postsepsis was approximately 25 mmHg lower than that observed at baseline. However, despite the decrease in LVESP, LVESD was unchanged. On the other hand, when hemofiltration was performed in group 2, LVESD decreased significantly between 4 and 6 h postsepsis, whereas LVESP decreased slightly but not significantly during this interval. In group 3, phenylephrine was added at 4 h postsepsis, and both LVESD and LVESP increased compared with measurements obtained at

Table 2. Cardiac Mechanics in the Four Groups (n = 5)

	LVEDD (cm)	LVESP (mmHg)	LVESD (cm)
Group 1			
Baseline	4.2 ± 1.0	137 ± 16	2.5 ± 0.8
4 h	4.1 ± 1.0	109 ± 12*	2.5 ± 0.8
6 h	4.1 ± 1.0	109 ± 21*	2.6 ± 1.0
Group 2			
Baseline	3.3 ± 0.6	124 ± 14	2.6 ± 0.4
4 h	3.2 ± 0.8	97 ± 15*	2.6 ± 0.4
6 h	3.3 ± 0.8	88 ± 10*	2.4 ± 0.3†
Group 3			
Baseline	3.7 ± 0.9	124 ± 15	1.8 ± 0.7
4 h	3.6 ± 0.9	86 ± 30†	1.7 ± 0.8
6 h	3.6 ± 0.9	117 ± 11‡	1.9 ± 0.8†
Group 4			
Baseline	3.6 ± 1.0	127 ± 24	1.8 ± 0.9
4 h	3.5 ± 1.0	96 ± 15†	1.7 ± 0.9
6 h	3.5 ± 0.9	118 ± 19‡	1.6 ± 0.9†§

Values are mean ± SD.

LVEDD and LVESD = left ventricular end-diastolic and end-systolic dimensions, respectively; LVESP = left ventricular end-systolic pressure.

* $P < 0.05$ *versus* baseline in group (by within groups ANOVA and SNK).

† $P < 0.05$ *versus* other conditions in a group.

‡ $P < 0.05$ change 4 to 6 h *versus* group 1 and 2 by between groups ANOVA and SNK.

§ $P < 0.05$ change 4 to 6 h in group 3 *versus* group 4.

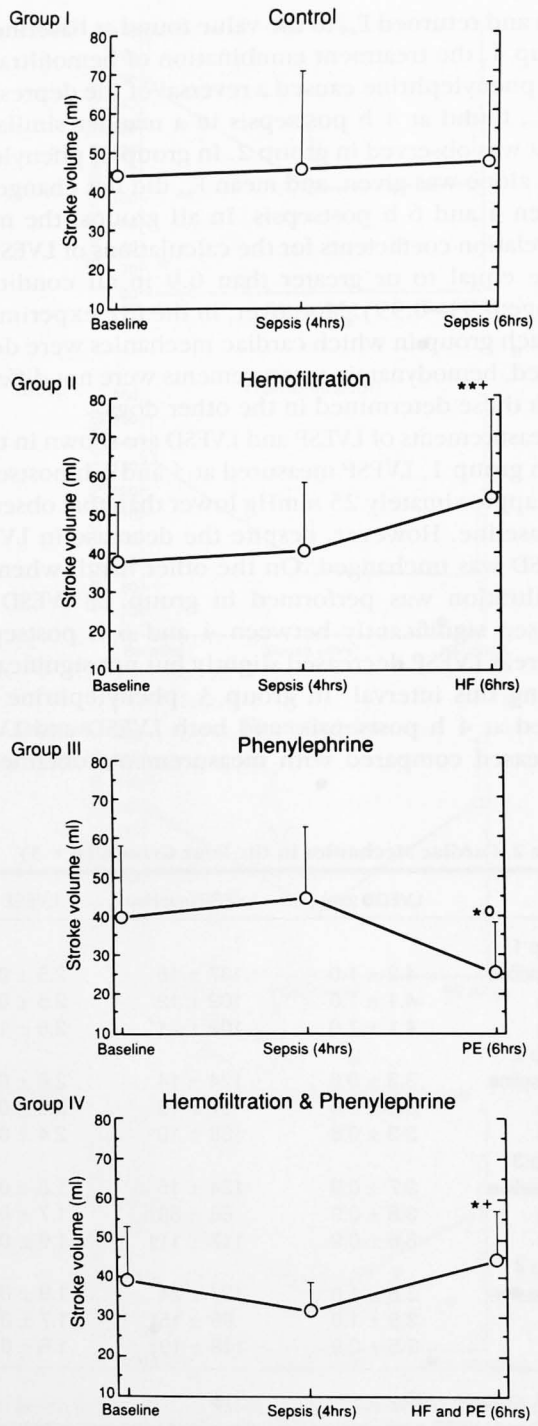


Fig. 2. Mean (±SD; n = 10) stroke volumes in the four groups at baseline, 4 h postsepsis, and 6 h postsepsis. In group 1, SV was unchanged between conditions. In group 2 (hemofiltration [HF]) and group 4 (HF and phenylephrine [PE]), SV increased after treatment. In group 3, SV decreased when PE alone was instituted. *$P < 0.05$ *versus* 4 h and **$P < 0.05$ *versus* other conditions within a group by repeated-measures analysis of variance and Student-Newman-Keul analysis; +$P < 0.05$ *versus* groups 1 and 3 and ○$P < 0.05$ *versus* other groups in which the respective changes in stroke volume between 4 and 6 h in the four groups are compared by one-way between-groups analysis of variance and Student-Newman-Keul analysis.

baseline and 4 h postsepsis. Finally, in group 4, LVESD decreased significantly between 4 and 6 h postsepsis, even though LVESP was significantly increased with phenylephrine. The results obtained in LVESD between 4 and 6 h postsepsis in group 4 were significantly different from those in group 3.

In the four groups, SVR obtained during the three conditions are shown in table 1. Compared with that measured at baseline, SVR decreased to varying extents at 4 h postsepsis in all groups. In group 3, it can be seen that when phenylephrine was infused, SVR significantly increased between 4 and 6 h postsepsis, and the increase in BP due to phenylephrine was associated with a further decrease in CO. In contrast, when phenylephrine was infused in group 4, SVR was unchanged between these two measurement periods because CO increased along with BP in response to hemofiltration. There were no changes in PVR between conditions in any of the four groups.

Table 4 shows the arterial blood gas and hematocrit values in the four groups. By design, arterial P_{O_2} was maintained high so that hemoglobin would be approximately 100% saturated during all conditions. Hematocrit decreased over the course of the experiment, and changes in hematocrit between conditions were not different between groups (table 4). In addition, there was a progressive metabolic acidosis that occurred in all groups during the course experiment. Although variability in *p*H and P_{CO_2} is shown in table 4, during the respective conditions, there were no significant differences in these parameters among the four groups. Venous blood gas parameters obtained in the four groups are shown in table 5, and there were also no significant differences in these parameters among the four groups.

Parameters of tissue oxygen delivery are shown in table 6. In group 4, the decrease in tissue oxygen delivery observed between 4 and 6 h was significantly less than that in group 3. Moreover, in group 3, there was a significant increase in arterial − venous oxygen content difference between 4 and 6 h postsepsis compared with that found in group 4.

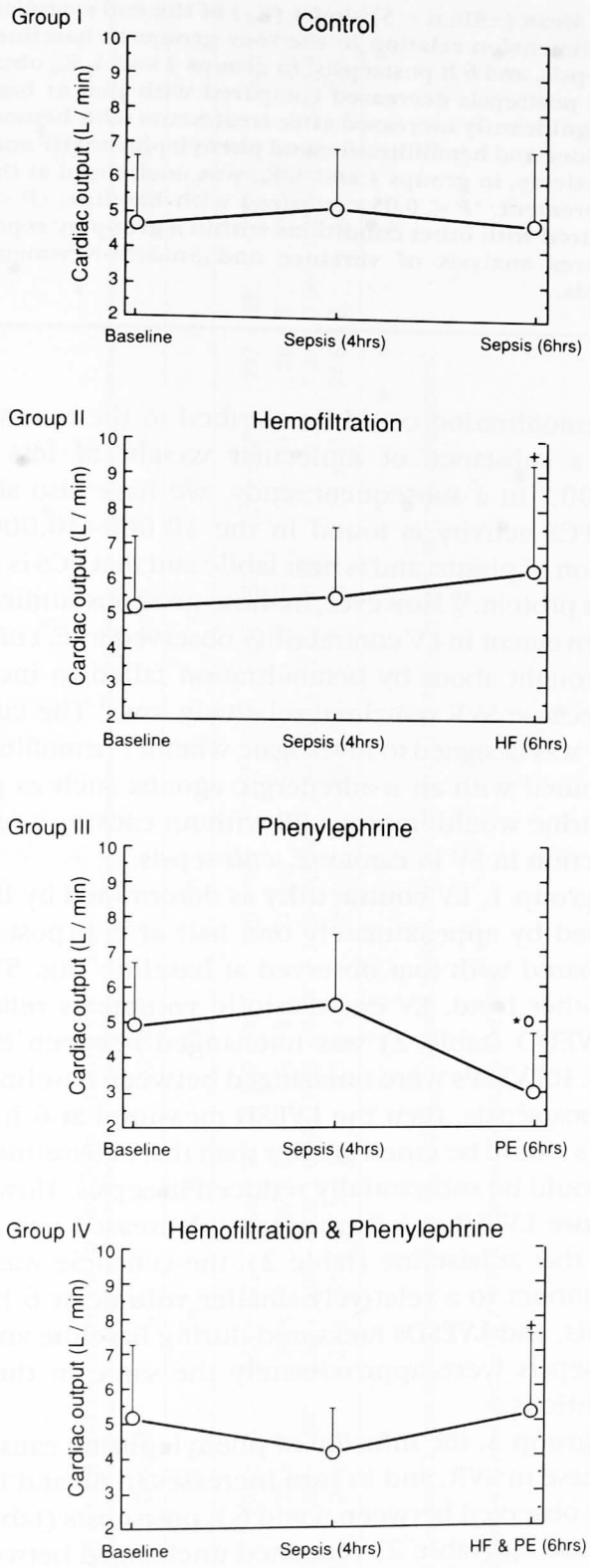


Fig. 3. Mean (±SD; n = 10) cardiac outputs in the four groups at baseline, 4 h postsepsis, and 6 h postsepsis. HF = hemofiltration; PE = phenylephrine. *$P < 0.05$ from baseline and 4 h postsepsis by repeated-measures analysis of variance; +$P < 0.05$ *versus* groups 1 and 3 and ○$P < 0.05$ *versus* other groups in which the respective changes in cardiac output observed between 4 and 6 h postsepsis in the four groups are compared by one-way between-groups analysis of variance and Student-Newman-Keul analysis.

Table 3. Hemodynamics in the Sham Hemofiltration Group (n = 7)

	Baseline	4 h Post-sepsis	Sham Hemofiltration
BP (mmHg)	146 ± 44	101 ± 13*	98 ± 12*
Pap (mmHg)	20 ± 4	21 ± 7	19 ± 4
Pwp (mmHg)	11 ± 4	12 ± 3	11 ± 2
Rap (mmHg)	5 ± 2	6 ± 2	5 ± 2
CO (L/min)	7.3 ± 3.3	7.9 ± 3.6	6.4 ± 2.7
SV (ml)	51 ± 21	66 ± 27	60 ± 24
HR (beats/min)	146 ± 52	112 ± 42	115 ± 43
PVR ($mmHg \cdot L^{-1} \cdot min^{-1}$)	1.5 ± 0.8	1.3 ± 1.1	1.2 ± 0.6
SVR ($mmHg \cdot L^{-1} \cdot min^{-1}$)	24 ± 19	14 ± 9	16 ± 8

Values are mean ± SD.

See Table 1 for abbreviations used.

* $P < 0.05$ from baseline by repeated measures ANOVA and SNK.

Discussion

In groups 2 and 4, the reduction in LV contractility observed after 4 h of *E. coli* sepsis was reversed by hemofiltration. This finding is similar to the results obtained in a previous study in which we showed that reversal of depressed LV contractility in *E. coli* sepsis

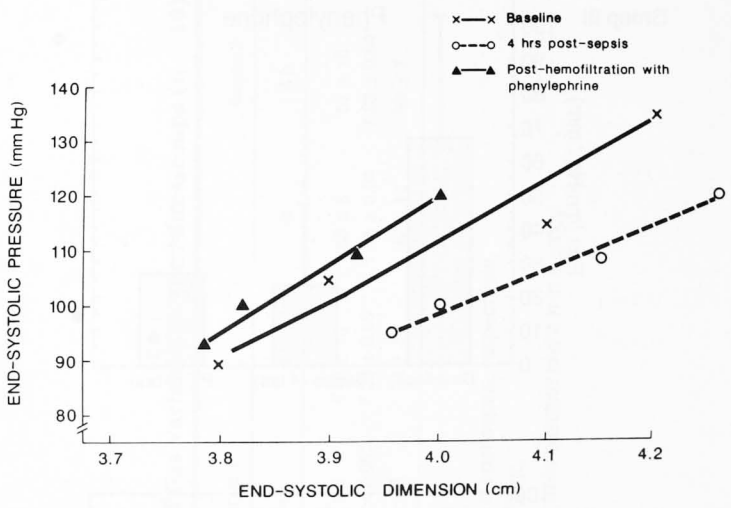
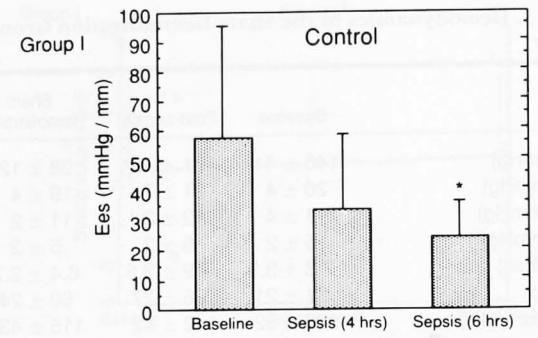
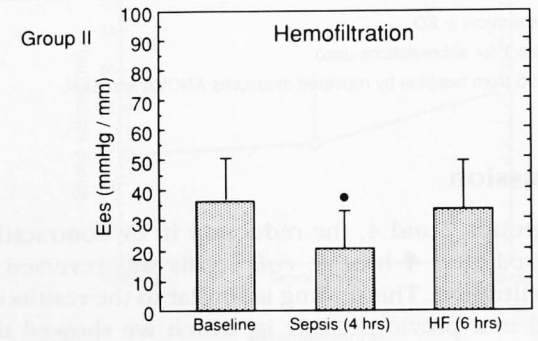
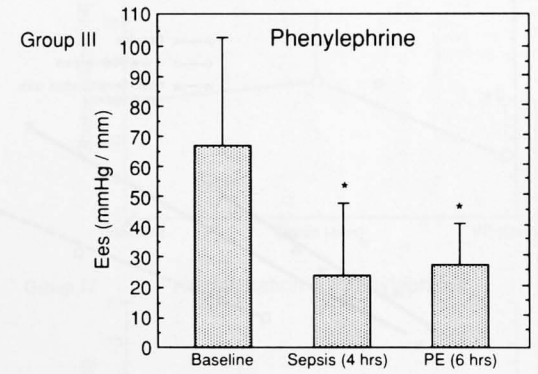


Fig. 4. Left ventricular end-systolic pressure–dimension relation in a dog in group 4 at baseline, 4 h postsepsis, and after treatment with hemofiltration and phenylephrine. End-systolic pressure is plotted on the ordinate and end-systolic dimension on the abscissa. Results were examined over a similar range of end-systolic pressures between conditions. The slope of the relation obtained by linear regression analysis defines left ventricular contractility. Compared with that found at baseline, the relation was shifted downward and to the right at 4 h postsepsis. This decrease in contractility was reversed after treatment with hemofiltration and phenylephrine. The correlation coefficients obtained at baseline, 4 h postsepsis, and 6 h postsepsis were 0.99, 0.99, and 0.97 respectively.







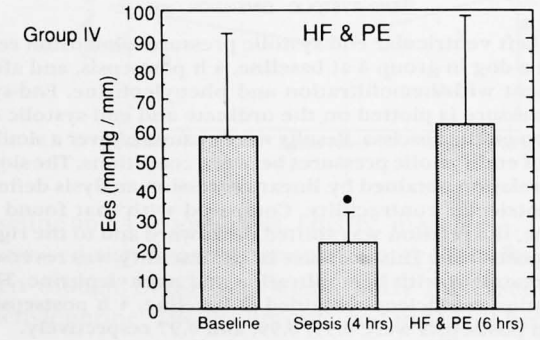


Fig. 5. Mean (±SD; n = 5) slopes (E_{es}) of the end-systolic pressure–dimension relation in the four groups at baseline, 4 h postsepsis, and 6 h postsepsis. In groups 2 and 4, E_{es} obtained at 4 h postsepsis decreased compared with that at baseline and significantly increased after treatments with hemofiltration alone and hemofiltration and phenylephrine (HF and PE), respectively. In groups 1 and 3, E_{es} was unchanged at the 6-h measurement. *$P < 0.05$ compared with baseline; •$P < 0.05$ compared with other conditions within a group by repeated-measures analysis of variance and Student-Newman-Keul analysis.

by hemofiltration could be ascribed to the removal of FCS, a substance of molecular weight of less than 30,000.[4] In a subsequent study, we have also shown that FCS activity is found in the 10,000–30,000–Da fraction of plasma and is heat labile and that FCS is probably a protein.[16] However, in those previous studies, the improvement in LV contractility observed in *E. coli* sepsis brought about by hemofiltration failed to increase BP because SVR remained relatively low.[4] The current study was designed to investigate whether hemofiltration combined with an α-adrenergic agonist such as phenylephrine would improve BP without causing a serious reduction in SV in canine *E. coli* sepsis.

In group 1, LV contractility as determined by E_{es} decreased by approximately one half at 6 h postsepsis compared with that observed at baseline (fig. 5). On the other hand, LV end-diastolic volume as reflected by LVEDD (table 2) was unchanged between conditions. If LVESPs were unchanged between baseline and 6 h postsepsis, then the LVESD measured at 6 h postsepsis would be much greater than that at baseline, and SV would be substantially reduced in sepsis. However, because LVESP at 6 h postsepsis decreased compared with that at baseline (table 2), the ventricle was able to contract to a relatively smaller volume at 6 h postsepsis, and LVESDs measured during baseline and 6 h postsepsis were approximately the same in the two conditions.

In group 3, the infusion of phenylephrine caused an increase in SVR, and in turn increases in BP and LVESP were observed between 4 and 6 h postsepsis (table 2). Because E_{es} (table 2) remained unchanged between 4 and 6 h postsepsis (fig. 5), the effect of this increase in LVESP on cardiac mechanics was to reduce the extent to which the ventricle could contract at 6 h postsepsis. Because LVEDD did not change between conditions and because LVESD increased at 6 h postsepsis, this reduction in fractional shortening resulted in a decrease in SV at the 6-h point in group 3.

Table 4. Arterial Blood Gases and Hematocrit in the Four Groups (n = 10)

	Group 1			Group 2			Group 3			Group 4		
	B	4 h	6 h	B	4 h	6 h	B	4 h	6 h	B	4 h	6 h
P_{O_2} (mmHg)	264 ± 69	201 ± 63	163 ± 92†	299 ± 96	237 ± 111	179 ± 90†	257 ± 36	238 ± 67	210 ± 80*	297 ± 38	178 ± 94*	189 ± 87*
P_{CO_2} (mmHg)	34 ± 4	31 ± 4*	26 ± 2†	32 ± 5	29 ± 5	21 ± 4†	31 ± 4	28 ± 5	24 ± 6†	36 ± 5	29 ± 8*	18 ± 4†

Table 4. Arterial Blood Gases and Hematocrit in the Four Groups (n = 10)

	Group 1			Group 2			Group 3			Group 4		
	B	4 h	6 h	B	4 h	6 h	B	4 h	6 h	B	4 h	6 h
P_{O_2} (mmHg)	264 ± 69	201 ± 63	163 ± 92†	299 ± 96	237 ± 111	179 ± 90†	257 ± 36	238 ± 67	210 ± 80*	297 ± 38	178 ± 94*	189 ± 87*
P_{CO_2} (mmHg)	34 ± 4	31 ± 4*	26 ± 2†	32 ± 5	29 ± 5	21 ± 4†	31 ± 4	28 ± 5	24 ± 6†	36 ± 5	29 ± 8*	18 ± 4†
*p*H	7.37 ± 0.04	7.32 ± 0.04*	7.36 ± 0.06	7.38 ± 0.04	7.28 ± 0.04*	7.29 ± 0.04*	7.39 ± 0.04	7.32 ± 0.05	7.31 ± 0.02	7.37 ± 0.04	7.30 ± 0.86	7.36 ± 0.11
HCT	31 ± 10	24 ± 7*	21 ± 11*	27.5 ± 12	21 ± 10*	18 ± 10*	29 ± 8	25 ± 9	23 ± 11	27.5 ± 6	26 ± 8	20 ± 7

Values are mean ± SD.

B = baseline; 4 h and 6 h = 4 and 6 h post-sepsis, respectively. P_{O_2} and P_{CO_2} = arterial oxygen and carbon dioxide tensions, respectively; Hct = hematocrit.

* $P < 0.05$ from baseline.

† $P < 0.05$ *versus* baseline and 4 h. All statistics by ANOVA repeated measures and SNK.

Table 5. Mixed Venous Blood Gas Variables in the Four Groups (n = 10)

	Group 1			Group 2			Group 3			Group 4		
	B	4 h	6 h	B	4 h	6 h	B	4 h	6 h	B	4 h	6 h
MVP_{O_2} (mmHg)	53 ± 10	55 ± 6	46 ± 10	55 ± 8	57 ± 16	51 ± 17	48 ± 8	55 ± 11	45 ± 13	55 ± 10	52 ± 11	50 ± 11
*p*H	7.34 ± 0.04	7.29 ± 0.05*	7.29 ± 0.05*	7.34 ± 0.04	7.23 ± 0.04*	7.24 ± 0.05*	7.36 ± 0.04	7.27 ± 0.06*	7.25 ± 0.05*	7.32 ± 0.04	7.27 ± 0.05	7.25 ± 0.05
P_{CO_2} (mmHg)	39 ± 5	38 ± 3	34 ± 1*	42 ± 10	39 ± 7	30 ± 5.6†	35 ± 4	35 ± 5	31 ± 6†	40 ± 5	37 ± 12	32 ± 11

Values are mean ± SD.

B = baseline; 4 h and 6 h = 4 and 6 h post-sepsis, respectively.

By repeated measures ANOVA and SNK,

* $P < 0.05$ from baseline; †$P < 0.05$ from baseline and 4 h in a group.

Table 6. Tissue Oxygen Delivery in the Four Groups (n = 10)

	Group 1			Group 2			Group 3			Group 4		
	B	4 h	6 h	B	4 h	6 h	B	4 h	6 h	B	4 h	6 h
Oxygen deliver (ml/min)	650 ± 350	560 ± 190	420 ± 170*‡	750 ± 390	590 ± 260	540 ± 290‡	590 ± 220	630 ± 320	350 ± 210†	650 ± 300	500 ± 150	510 ± 150‡
$(A\text{-}V)O_2$ (ml/100ml)	3.8 ± 1.6	2.8 ± 0.9*	3.3 ± 0.9	3.3 ± 1.0	2.5 ± 1.0*	2.3 ± 0.9*	3.9 ± 1.2	2.6 ± 1.0*	3.1 ± 1.5	3.0 ± 0.7	3.2 ± 1.4	2.4 ± .3‡§

Values are mean ± SD.

B = baseline; 4 h and 6 h = 4 and 6 h post-sepsis, respectively; $(A\text{-}V)O_2$ = arterial minus venous oxygen content difference.

By repeated measures ANOVA and SNK, *$P < 0.05$ from baseline in a group; †$P < 0.05$ from baseline and 4 h.

By between ANOVA and SNK, ‡$P < 0.05$ change between 4 and 6 h *versus* group 1.

By between ANOVA and SNK, §$P < 0.05$ change between 4 and 6 h is different from that in group 3.

On the other hand, in groups 2 and 4, hemofiltration reversed the reduction in LV contractility found at the 4-h point. In group 2, the reduction in LVESD observed with hemofiltration in table 2 is similar to that previously described.[4] In group 4, combined therapy with hemofiltration and phenylephrine was instituted. Compared with measurements obtained at 4 h postsepsis, both E_{es} and LVESP were increased at 6 h postsepsis in group 4. These increases would have opposite effects on SV: because of an increase in contractility, an increase in E_{es} would result in an improvement in ventricular emptying, whereas an increase in LVESP would cause a reduction in emptying. In group 4, the net result was that SV obtained at 6 h postsepsis was improved compared with that observed at 4 h postsepsis and was now similar to that determined at baseline. It should be noted, however, that if the relative increase in LVESP caused by phenylephrine were to occur to a much greater extent than the improvement in E_{es} caused by hemofiltration, then SV could decrease when the combination of the two treatments was implemented.

Our results also show that the decrease in tissue oxygen delivery that was observed when phenylephrine was added in group 3 was prevented by hemofiltration. In group 3, mean tissue oxygen delivery decreased from 650 ml/min at 4 h to 350 ml/min at 6 h postsepsis (table 6). On the other hand, in group 4, tissue oxygen delivery was not changed between 4 and 6 h. The changes in tissue oxygen delivery and arterial − venous content differences were significantly different between groups 3 and 4.

In the current study, the index of LV contractility used was E_{es}, and there are aspects of our use of this index that require comment. Calculation of E_{es} was based on changes observed along the anterior–posterior axis alone; changes in dimensions along the apex–base and septal–lateral axes were not determined. This measurement method was selected because our previous study indicated that all LV axes showed similar systolic and diastolic changes in sepsis.[4] Little *et al.*[14] also found that LV end-systolic pressure–volume and pressure–dimension changes showed similar results in the assessment of global changes in contractility. Therefore, we did not feel that insertion of an additional two crystal pairs would contribute significantly more information to the study.

As shown in figure 5, there was also wide variability in E_{es} between animals, because E_{es} is not indexed to heart size and is dependent on the relative distance between crystal pairs. Among animals of all sizes,

LVESPs are fairly uniform. On the other hand, for given changes in LVESP, the respective changes in LVESD would be dependent on the size of the animal and the exact crystal placement in addition to the contractile state of the muscle. Because of this wide variability in baseline E_{es} between animals, our analysis and conclusions are based the changes in these parameters between conditions in the respective groups.

It is also important to recognize that in a previous study,[4] we showed that hemofiltration did not change E_{es} in nonseptic dogs, and therefore the improvement in E_{es} observed in *E. coli* sepsis is not a nonspecific effect of hemofiltration on cardiac mechanics. In that study, we also showed that in sepsis the reversal of cardiac depression by hemofiltration could not be explained by changes in serum pentobarbital concentrations or in serum free calcium concentrations, because both were measured and were unchanged before and after hemofiltration.[4] In the current study, we further showed in the sham hemofiltration group (table 3) that by simply connecting the animal to the hemofiltration circuit in an attempt to unload the LV for a 2-h period did not improve SV in sepsis.

In each of the four groups, moreover, we examined hemodynamics in all dogs; cardiac mechanics were examined only in half of the animals. Because the number of experiments varied, this accounts for some differences observed between the cardiac and hemodynamic measurements. For instance, the results show that under baseline conditions, mean BP measured in groups 1 and 3 where n = 10 were higher than values of the corresponding LVESPs where n = 5.

From table 4, it can be observed that a metabolic acidosis develops over the course of sepsis in this model. In the current study, *p*H was restored toward normal by means of hyperventilation (*i.e.,* respiratory compensation) rather than by infusion of bicarbonate. We chose hyperventilation because intravenous bicarbonate administration to correct the acidosis made maintenance of constant pulmonary wedge pressure more difficult between conditions. Although P_{CO_2} and *p*H varied under the different conditions in table 4, there were no differences in blood gas parameters between groups. It must also be recognized that during hemofiltration, bicarbonate was filtered, and this anion was given back to the animal in the form of Ringer's lactate. It was sometimes difficult to infuse the Ringer's lactate at a rate equal to that at which bicarbonate was filtered. This would contribute to the slight differences in acid–base parameters observed between groups.

Although a greater degree of tissue acidosis was not observed in group 3 at the 6-h point (tables 4 and 5), the arterial − venous content difference in this group increased between 4 and 6 h postsepsis compared with that observed in group 4. Thus, even though tissue oxygenation was still relatively preserved in group 3, delivery was more precariously maintained than what was found in the hemofiltration groups, and hemofiltration could improve tissue acidosis under conditions in which tissue oxygen delivery was not preserved in sepsis.

It should also be noted that during hemofiltration, the flow rates of 2–3 l/min used in the current study are an order of magnitude higher than would be clinically obtained, so that the extrapolation of this data to the clinical setting is limited. Presumably, a longer duration of hemofiltration would need to be performed to obtain comparable results in the clinical situation.

In the current study, we showed that when phenylephrine was infused in group 3, there was a large reduction in CO compared with that found preinfusion. In contrast, others have found that when phenylephrine was administered to patients in septic shock, although SVR and BP were found to increase, a decrease in CO was not observed.[17,18] These results may be discrepant because in these clinical studies an increase in contractility occurred with phenylephrine because of α-adrenergic stimulation or enhanced coronary blood flow. Alternatively, the results may differ because clinical septic shock is primarily a high-CO state, as opposed to the normal CO state in the current study, and therefore the effects of vasopressors may differ in the two situations. Finally, it is possible that because contractility was relatively normal before the initiation of vasoconstriction therapy in these clinical studies, CO did not decrease when phenylephrine was added.

On the other hand, there was a severe reduction in LV contractility observed in the current study, and compared with baseline values, E_{es} decreased in all groups at the 4-h point by approximately one-half (fig. 5). Because of this severe decrease in LV contractility, the LV was very sensitive to an increase in afterload, and when BP was increased by phenylephrine, a marked reduction in CO and tissue oxygen delivery occurred. In contrast, when this depression in LV contractility was restored to normal by hemofiltration, phenylephrine was instituted without a significant reduction in tissue oxygen delivery.

In sepsis, one or more substances are released into plasma, leading to a reversible reduction in LV con-

tractility; other mediators cause systemic vasodilation by reducing SVR.[4] Our results show that in experimental sepsis, it is possible to maintain relatively normal SV and BP despite depressed LV contractility by means of a combination treatment approach that addresses each of these two mechanisms. Hemofiltration appears to reverse the depression in LV contractility observed in sepsis by removal of FCS activity, whereas phenylephrine maintains BP by increasing SVR. Although the relevance of animal models to human disease must be viewed with caution, our results suggest that in sepsis, combined treatment with hemofiltration and vasoconstricting agents may be useful in the treatment of depressed LV contractility and hypotension in sepsis.

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What I Have Learn

Lawrence J. Saidman, M.D.

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