Mechanisms for the High Circulatory Requirements in Sepsis and Septic Shock

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SEPSIS [1, 8] and septic shock [9, 27] are often accompanied by raised cardiac output, hypotension and low total peripheral vascular resistance. The basis for this is still unclear. It has been suggested that the additional energy requirements accompanying fever and sepsis may largely account for this circulatory state, yet there is often a great discrepancy between the large increase in cardiac output and the relatively small increment in oxygen consumption. These observations, together with the finding that the mixed venous oxygen content is often raised in septic patients, suggests that other mechanisms may be worthy of consideration. Local arterio-venous shunting within the septic region, a general cytotoxic effect, or augmented sympathetic drive, have all been proposed in explanation of this hyperdynamic circulatory state.

The present study evaluates the circulatory response to sepsis in dogs. It will be shown that neither elevated energy requirements due to sepsis and fever nor increased blood flow through the septic region can account for the extra cardiac output seen in this state. The explanation is rather to be found in the release of a powerful vasodilator from the septic region, which causes a considerable reduction in vascular resistance and increase in blood flow within the area of sepsis, the kidneys, and splanchnic organs.

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Materials and Methods

Healthy mongrel dogs * weighing 10–36 Kg. were used in these experiments. All studies and procedures were performed under light sodium thiopental sedation and local anesthesia using 1% Xylocaine. The animals were initially induced with 100 to 300 mg. sodium thiopental intravenously and supplemental sedation was provided as needed by saline drip containing 3 mg. sodium thiopental per ml. normal saline.

Systemic oxygen consumption was measured over a 45-minute period using a continuous oxygen consumption recorder.[17] During this period the animals were ventilated with a volume respirator attached to a cuffed endotracheal tube. A steady state was readily obtained under these conditions and this value taken as the oxygen consumption of the animal under these conditions.

Arterial and venous blood P_{O_2}, P_{CO_2} and pH were measured at 38.5° C. with an Instrumentation Laboratory pH/blood gas analyzer. pH, P_{O_2}, P_{CO_2} and HCO_3^- values were not corrected for temperature when the animal's rectal temperature varied from that of the pH/blood gas analyzer. Percentage hemoglobin saturation was determined by an American Optical Reflexion Oximeter. Hemoglobin concentration in Gm./100 ml. of blood was determined with the Hycel cyanomethemoglobin reagent and standard, and hematocrit by the micro-

* All animals were cared for in accordance with the regulations prepared by the Committee for Laboratory Animal Facilities and Care, NIH.

hematocrit technic. Oxygen content of arterial and venous blood was calculated according to the formula:

$$\text{Oxygen content} = 1.34 \times \text{Hb conc.} \times \text{Hb sat.} + 0.003 \times P_{O_2}$$

Regional oxygen consumption was calculated using the Fick principle:

$$\text{Oxygen Consumption} = \text{A}-\text{V } O_2 \text{ diff.} \times \frac{\text{Flow}}{100 \text{ ml.}}.$$

Plasma bicarbonate was calculated from the equation:

$$HCO_3^- = 10^{(pH-6.10)} \times 0.0298\ P_{CO_2}.$$

Acid hemolized blood lactate and pyruvate levels were determined using the Sigma Chemical No. 726-UV and 826-UV methods. Temperature was measured per rectum by a mercury expansion thermometer.

Cardiac output was measured by the standard dye (Indocyanine Green) dilution technic. Curves were obtained using a 103 IR Gilford densitometer with a Harvard constant rate pump. At least 2 and frequently 3 curves were obtained in each animal over a 15-minute period. The curves were calculated according to Lilienfield's method[21] and the average used for the cardiac output. Individual cardiac outputs deviated an average of ±7% from the mean of the individual outputs for a given animal. Systemic blood pressure was measured with a Sanborn pressure transducer. Total peripheral vascular resistance (TPR) was calculated as follows:

$$\text{TPR} = \frac{\text{Mean Blood Pressure (mm. Hg)}}{\text{Cardiac Output (l./min.)}}.$$

Regional blood flow (femoral and renal were measured directly with a Carolina Medical square wave flow transducer. Frequent mechanical occlusion was carried out to determine baseline and correct for drift. Splanchnic blood flow was estimated by comparing A-V O_2 difference before and after sepsis. The assumption is made that oxygen consumption for these tissues either remains the same or increases. Renal and femoral vascular resistance was calculated from the ratio of mean blood pressure to regional blood flow per minute and is expressed as mm. Hg/ml./min.

For purposes of comparing animals of varying weights, surface area in square meters was calculated using the formula:

$$\text{m.}^2 = \text{Kg.}^{2/3} \times 0.112.$$

Cardiac index and oxygen consumption were expressed as l./min./m.^{2} and cc./min./m.^{2}, respectively.

A septic model was prepared by placing ten 5 cm. wicks of umbilical tape contaminated with the animal's own enteric flora subcutaneously and intramuscularly in one hind limb of the animal. Care was taken to place the wicks at least 6–8 cm. distal to the site where femoral artery blood flow was measured. Preliminary studies on the natural history of this lesion in six animals demonstrated a uniformly severe cellulitis limited to the leg. All animals survived. They were most ill after 48–96 hours and by 7 days were in the recovery stage following spontaneous drainage of local abscesses and extrusion of the foreign bodies. Attempts were made early in these studies to utilize pure *E. coli* organisms to induce localized sepsis. However, local blood and wound cultures taken 48 to 72 hours subsequent to the induction of the septic leg almost invariably showed a mixed flora of organisms comparable to that seen when the animal's own enteric flora were used. As in Albrecht and Clowes study,[1] enteric organisms (*E. coli,* Pseudomonas) predominated in the septic leg. In addition, and to a lesser degree, Staphylococci and Streptococci along with a variable array of saphrophytes and other pathogens were also present.

Animals were arbitrarily classified in this study as responders (greater than 20% in-

crease in cardiac output with sepsis over that observed in the control state) and non-responders (less than 20% increase or a decrease in cardiac output with sepsis). No animals were included in these studies if there was evidence of sepsis beyond the groin of the septic leg or if control cardiac indices were less than 2.0 or greater than 5.0 l./min./m.^{2} Animals with a control rectal temperature greater than 39 centigrade degrees or a hematocrit value less than 30% were also eliminated from the study.

The arithmetic mean and standard error (S. E.) for each measured or calculated variable were determined. The value of the control variable was compared to the value of the response observed with sepsis by using the paired "t" test. No attempt was made to compare statistically the variables of responding animals with non-responding animals because of the small number of subjects in the latter group in our series. All mean values in this study were rounded off to the appropriate number of significant figures for the method used.

Protocol for Systemic Studies

Twenty-four animals weighing an average of 26.7 Kg. (approximately one m.^{2} surface area) underwent paired studies in the non-septic (control) and septic state. In a fasting, control state, animals were induced with sodium thiopental and a cuffed endotracheal tube was inserted into the trachea. Oxygen consumption was continuously recorded for 45 minutes and rectal temperature measured during this period. The endotracheal tube was then removed and the dogs allowed to breath spontaneously. Small 1–2 cm. incisions under local anesthesia and sterile conditions were made over the right external jugular vein, left brachial artery and over one of the femoral arteries. An appropriately sized square wave flow transducer was placed about the femoral artery just proximal to the profunda branch. Catheters were placed into the superior vena cava and left brachial artery and cardiac output was measured. Blood pressure, femoral blood flow and pulse rate were determined immediately following the measurement of cardiac output. Arterial and femoral venous blood were drawn for measurement of lactate, pyruvate, pH, P_{CO_2}, P_{O_2}, hematocrit, hemoglobin saturation and concentration during this period. Care was taken not to administer any sodium thiopental during or 10 minutes preceding the measurement of cardiac output and femoral blood flow since this substance has vasodilating effects on skeletal muscle and alters cardiac output. Following these measurements, the incisions were approximated with 4-0 silk. Then the standard septic lesion was induced in one hind limb and after a period of 48–72 hours these animals were re-evaluated in exactly the same manner as before. In addition, blood flow and O_2 consumption were determined in the septic and non-septic hind limb.

Protocol for Determining Renal Blood Flow

Ten animals weighing an average of 27.9 Kg. were sedated with sodium thiopental and cardiac output determined as previously mentioned. In addition, right kidney blood flow was measured directly with a square wave flow transducer. The 11th and 12th dermatome regions were blocked with 1% xylocaine under sterile conditions and a 10 to 12 cm. right flank incision was made just inferior to the last palpable rib. The right kidney was approached posteriorly and the renal artery was readily available with minimal manipulation so that a flow transducer could be applied. Right kidney blood flow was recorded continuously for 5 minutes. Immediately following the measurement of renal blood flow, arterial blood was drawn for determination of pH, P_{CO_2}, P_{O_2}, hematocrit, hemoglobin saturation and concentration. The incisions were closed and a septic leg induced by the standard

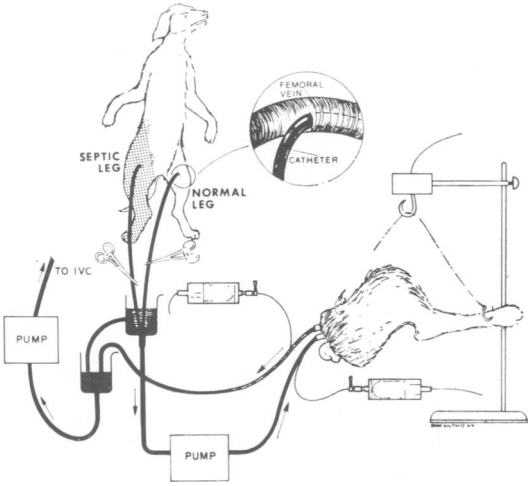

FIG. 1. The isolated perfused hind limb model used to test for the presence of vasodilator substances in septic leg venous blood.

method in eight animals while the remaining two animals served as controls. Forty-eight to 72 hours later, the measurements were repeated.

Protocol for Estimating Splanchnic Blood Flow

Eight animals weighing an average of 15.8 Kg. had portal vein and abdominal aorta catheters chronically implanted for the purpose of serially monitoring A-V O_2 difference across the splanchnic organs in the conscious state. A-V O_2 difference in volumes per cent was determined daily under fasting conditions. Following a 72-hour control period, the animals were induced with sodium thiopental, cardiac output determined and the septic leg induced. The animals were then monitored daily in the septic state. Again after 72 hours of sepsis, the animals were induced with sodium thiopental and cardiac output determined.

The assumption was made that oxygen consumption of the splanchnic organs either remained the same or increased with sepsis. A narrowing of the A-V O_2 difference, making this assumption, would indicate an increase in blood flow through this region. Therefore, the minimal per cent increase in splanchnic blood flow with sepsis over control flow was calculated according to the following formula:

$$\frac{\text{Control A}-\text{V } O_2 \text{ diff.} - \text{Septic A}-\text{V } O_2 \text{ diff.}}{\text{Septic A}-\text{V } O_2 \text{ diff.}} \times 100.$$

Protocol for Vasoactive Studies

(a) *Isolated Leg Perfusion Experiments:* Seven animals with the standard septic leg were prepared under sodium thiopental sedation and local anesthesia as shown in Figure 1. Bilateral non-occluding femoral vein catheters were placed as shown in the insert in Figure 1. An isolated perfused hind limb from a small puppy weighing 3–3.5 Kg. was used to test for differences in vasoactivity in arterial, septic venous blood and non-septic venous blood. Constant perfusion of the leg with arterial blood and femoral venous blood from the septic and non-septic leg was carried out with a sigmamotor pump while arterial perfusion and venous pressure were measured continuously with Sanborn pressure transducers. A change in perfusion pressure using this model indicates a change in vascular resistance since flow was held constant. The perfusate was altered every 30 minutes. Isolated leg oxygen consumption was determined just prior to switching perfusates. This preparation eliminated the effect of nervous influences on the test preparation.

(b) *Intact Contralateral Leg Infusion Experiments:* In this model, the intact non-septic hind limb was used as the test preparation. Thirteen animals, nine of which underwent paired systemic studies, were prepared as depicted in Figure 2. Bilateral non-occluding cannulas were placed in the femoral veins. A small branch of the non-septic leg femoral artery was cannulated with 0.062 inch I.D. polyethylene tubing. A constant amount (40 cc./min.) of either non-septic or septic venous blood was infused with a sigmamotor pump into the

femoral artery. Proximal to the site of infusion, an appropriately sized and calibrated square wave flow transducer was placed to measure femoral artery blood flow. Infusions (non-septic or septic venous blood) were alternated every 20 minutes while femoral blood flow and systemic arterial blood pressure were recorded continuously on a Sanborn 4 channel recorder. Oxygen consumption of the non-septic leg was determined just prior to alternating infusions.

Results

1. Systemic Effects of Sepsis

The following experiments were carried out to evaluate the systemic energy requirements and the circulatory response to sepsis.

(a) *Hemodynamic Observations:* The detailed protocol for these experiments has already been given. In brief, 24 animals were evaluated by determining the following: 1) Pulse Rate 2) Blood Pressure, 3) Cardiac Output and 4) Total Peripheral Vascular Resistance before and 48–72 hours after induction of a septic hind leg. Fifteen of the 24 animals evaluated under control and septic conditions responded (20% or greater increase in cardiac output) according to the arbitrary standards set up in this study. Table 1 shows that the mean cardiac index increased from a control level of 3.2 to 4.8 l./min./m.^{2} with sepsis. Average pulse rate likewise increased from 133 to 165 beats/minute. Mean arterial blood pressure dropped from 128 to 102 mm. Hg while calculated total peripheral vascular resistance index decreased from 39 to 21 mm. Hg/l./min./m.^{2} Hematocrit did not vary significantly from the control value of 39%.

(b) *Metabolic Observations:* Table 2 reveals that mean rectal temperatures increased 1.3 centigrade degrees in the 15 responding animals with sepsis while mean systemic oxygen consumption increased

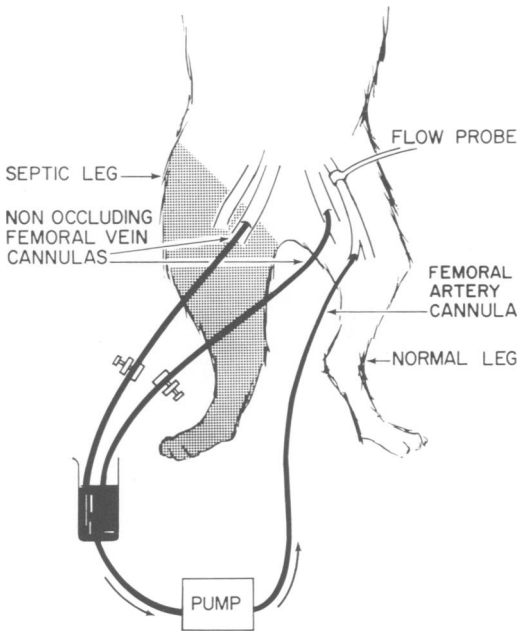

FIG. 2. The intact contralateral hind limb model used to test for the presence of vasodilator materials in septic leg venous blood.

12%. No significant changes occurred in arterial pH or hemoglobin saturation. Arterial P_{CO_2} and calculated plasma HCO_3^- significantly decreased with sepsis. Mean arterial blood lactate and pyruvate concentrations during the control state were 0.38 mM./l. and 0.046 mM./l., respectively, and showed no significant variation with sepsis. These findings show that sepsis under the conditions of this study caused a 50% (1,600 ml.) increase in cardiac index, 16% reduction in systemic blood pressure, 24% increase in pulse rate, 46% decrease in total peripheral vascular resistance index, 12% increase in systemic oxygen utilization and 1.3 centigrade degrees rise in rectal temperature. Taken together, these findings indicate that cardiac output is increased out of proportion to the energy needs in sepsis.

To determine the basis for the circulatory response to sepsis, altered sympathetic activity, blood flow through the septic region and other factors which disturb baroceptor activity by producing peripheral

TABLE 1. *Systemic Hemodynamic Response to Sepsis in 15 Responding Animals*

Measurements and Calculations	Control (mean ± S.E.)	*P* Value	Sepsis (mean ± S.E.)	%Δ
Pulse rate (beats/min.)	133 ± 9	<0.01	165 ± 6	+24
Arterial blood pressure (mm.Hg)	122 ± 3	<0.001	102 ± 5	−16
Cardiac index (l./min./m.²)	3.2 ± 0.2	<0.005	4.8 ± 0.3	+50
Total peripheral vascular resistance index (mm.Hg/l./min./m²)	39 ± 2	<0.001	21 ± 2	−46
Arterial hematocrit (%)	39 ± 1	N.S.	41 ± 2	—

vasodilation and hypotension need to be considered. The following studies take up some of these problems.

2. Local Effects of Sepsis

The possibility that heightened cardiac activity in sepsis results predominantly from increased blood flow distributed to the septic area is extremely intriguing. Albrecht and Clowes[1] using a septic hind limb model state that the blood flow through the septic region is "considerably greater than that to the opposite side." Moreover, they suggest that the inflammatory area may behave as a functional arterio-venous shunt thereby accommodating a large portion of the extra cardiac output observed in sepsis. The following studies were performed to evaluate blood flow and metabolic requirements of the septic region itself.

(a) *Hemodynamic Changes in the Septic and Non-Septic Leg:* The detailed protocol is presented in material and methods. Femoral blood flow was measured in the control state and 48–72 hours after induction of the septic leg. In addition femoral oxygen consumption was determined, as well as, other variables in the septic and non-septic venous blood. Table 3 summarizes the changes in femoral blood flow in the 15 responding animals before and after

TABLE 2. *Systemic Metabolic and Acid-Base Response to Sepsis in 15 Responding Animals*

Measurements and Calculations	Control (mean ± S.E.)	*P* Value	Sepsis (mean ± S.E.)	%Δ
Rectal temperature (°C.)	38.6 ± 0.2	<0.001	39.9 ± 0.2	—
Oxygen consumption (cc./min./m.²)	165 ± 4	<0.005	185 ± 4	+12
Arterial pH	7.41 ± .01	N.S.	7.43 ± 0.01	—
Arterial Hb SAT (%)	92 ± 1	N.S.	91 ± 1	—
Arterial P_{CO_2} (mm. Hg)	36 ± 2	<0.025	31 ± 1	—
Plasma HCO_3^- (mM./l.)	22 ± 1	<0.025	19 ± 1	—
Arterial blood lactate (8) (mM./l.)	0.38 ± 0.02	N.S.	0.36 ± 0.01	—
Arterial blood pyruvate (8) (mM./l.)	0.046 ± 0.005	N.S.	0.045 ± 0.008	—

( ) Number of animals other than 15.

TABLE 3. *Local Response to Sepsis in 15 Responding Animals*

Measurements and Calculations	Control (mean ± S.E.)	*P* Value	Sepsis (mean ± S.E.)	%Δ
Arterial blood pressure (mm.Hg)	122 ± 3	<0.001	102 ± 5	−16
Femoral artery blood flow (ml./min.)	150 ± 1	<0.005	† 91 ± 7	−39
		<0.001	* 272 ± 20	+81
Femoral vascular resistance (mm.Hg/ml./min.)	0.82 ± 0.07	<0.01	† 1.13 ± 0.08	+38
		<0.001	* 0.38 ± 0.03	−54
Femoral venous Hb SAT (%)	75 ± 2	<0.01	† 69 ± 1	−8
		<0.025	* 81 ± 1	+8
Femoral oxygen consumption (cc./min.)	4.1 ± 0.3	N.S.	† 3.8 ± 0.3	−7
		<0.05	* 4.9 ± 0.4	+20
Femoral venous blood lactate (8) (mM./l.)	0.36 ± 0.02	N.S.	† 0.37 ± 0.01	—
		<0.05	* 0.47 ± 0.04	—
Femoral venous blood pyruvate (8) (mM./l.)	0.046 ± 0.007	N.S.	†0.045 ± 0.006	—
		<0.10	*0.064 ± 0.013	—

( ) Number of animals other than 15.
* Septic leg.
† Adjacent non-septic leg.

sepsis. Control femoral blood flow averaged 150 ml./min. and increased to 272 ml./min. (81% increase) in the septic leg. In contrast, blood flow in the contralateral leg decreased to 91 ml./min. (39% decrease). Femoral vascular resistance decreased 54% in the septic leg and increased 38% in the opposite non-septic hind limb.

(b) *Metabolic Data:* Table 3 reveals a mean control hind leg oxygen consumption of 4.1 cc./min. After 48–72 hours of sepsis, oxygen consumption significantly increased to 4.9 cc./min. (20% increase) in the septic leg. In contrast, oxygen consumption in the contralateral non-septic leg did not change significantly. Mean femoral venous lactate for the control leg was 0.36 mM./l. and after sepsis increased to 0.47 mM./l. in septic leg femoral venous blood while remaining at 0.37 mM./l. in the opposite non-septic leg femoral venous blood. The femoral venous pyruvate values for the same vascular beds averaged 0.046 mM./l. in the control state and 0.064 and 0.045 mM./l. in the septic leg and contralateral non-septic leg, respectively. The femoral venous hemoglobin saturation increased from 75% to 81% in the septic leg while falling to 69% in the non-septic leg.

Together, these studies show that flow increases 81% in the septic leg, while oxygen demands rise only 20%. That the increased flow largely reflects vasodilation rather than shunting is suggested by the small increase in lactate production by the septic leg. Of great interest is the finding that blood flow falls in the contralateral non-septic leg and probably in muscle and skin generally and that the increment in blood flow through the septic leg is small in comparison with the considerable increase in cardiac output. These data indicate that there must be diversion to and increased flow in some core areas in sepsis. Accordingly, the following studies were carried out to determine the distribution of the additional cardiac output in sepsis.

3. Distribution of Blood Flow with Sepsis

Little is known about the effects of sepsis on distribution of cardiac output. The following studies were carried to examine this problem.

(a) *Renal Blood Flow:* To reiterate briefly, right kidney blood flow was measured with an electromagnetic flow transducer before and after sepsis in eight animals. Another two animals served as con-

TABLE 4. *Effects of Sepsis on Renal Hemodynamics in 8 Animals*

Measurements and Calculations	Control (mean ± S.E.)	*P* Value	Sepsis (mean ± S.E.)	%Δ
Arterial blood pressure (mm./Hg)	146 ± 8	<0.0025	108 ± 5	−26
Cardiac output (l./min.)	3.4 ± 0.1	N.S.	3.7 ± 0.2	+9
Total peripheral vascular resistance (mm.Hg/l./min.)	43 ± 3	<0.005	29 ± 3	−33
Right kidney blood flow (ml./min.)	265 ± 26	<0.005	425 ± 37	+60
Right kidney vascular resistance (mm.Hg/ml./min.)	0.55 ± 0.07	<0.0025	0.25 ± 0.03	−55
Hematocrit (%)	40 ± 2	N.S.	42 ± 2	—

trols and underwent the same procedure without induction of the septic leg to evaluate the effects of manipulation on kidney blood flow. Table 4 shows that mean right kidney blood flow, measured directly, increased from 265 ml./min. to 425 ml./min. (60% increase) with sepsis, while calculated right kidney vascular resistance decreased 55% demonstrating clearly an increase in vascular dimensions or the opening of unperfused channels in this vascular bed. Note that cardiac output did not increase significantly with sepsis under these conditions (Table 4). The addition of the abdominal flank incision, with induction of the septic leg, made the animals more ill and led to decreased fluid intake, dehydration and severe hemoconcentration in four of the eight animals. No significant change in renal blood flow was noted in the two control animals.

(b) *Estimated Splanchnic Blood Flow:* The protocol for estimating splanchnic blood flow is outlined in materials and methods. The assumption was made that since systemic oxygen consumption increased 12% with sepsis, that the oxygen consumption of splanchnic organs either remained the same or increased with sepsis. Therefore, a narrowing of the A-V O_2 difference across this vascular bed would indicate an increase in blood flow. Table 5 shows that mean splanchnic A-V O_2 difference in 8 animals averaged 2.92 volumes per cent before sepsis and 2.11 volumes per cent after 48 hours of sepsis. This suggests that splanchnic blood flow increased a minimum of 38% with sepsis. Note that mean cardiac output increased (42%) in these animals despite an abdominal flank incision. Hemoconcentration did not take place in any of these animals since induc-

TABLE 5. *Effects of Sepsis on Estimated Splanchnic Blood in 8 Animals*

Measurements and Calculations	Control (mean ± S.E.)	*P* Value	Sepsis (mean ± S.E.)	%Δ
Arterial blood pressure (mm.Hg)	113 ± 8	<0.025	89 ± 2	−21
Cardiac output (l./min.)	2.4 ± 0.2	<0.025	3.4 ± 0.3	+42
Total peripheral vascular resistance (mm.Hg/l./min.)	47 ± 4	<0.005	26 ± 2	−45
Estimated splanchnic blood flow (A−V O_2 Diff., Vol. %)	2.92 ± 0.18	<0.005	2.11 ± 0.17	+38
Hematocrit (%)	39 ± 2	N.S.	37 ± 1	—

tion of the septic leg was delayed 3 days after surgery.

These results show clearly that blood flow is increased in the kidneys (60% increase), splanchnic organs (38% increase) and in the area of sepsis (81% increase) while decreasing (39%) through non-septic skeletal muscle and probably skin. These findings prompted a search for a vasodilator substance capable of inducing the low resistance state seen in sepsis.

4. Release of Vasodilator Substances from the Septic Leg

The following studies were carried out in an effort to find a vasodilator substance released from the septic region.

(a) *Demonstration of a Vasodilator Substance Using the Intact Contralateral Leg:* The technic has been detailed in materials and methods. In brief, 40 ml./min. of non-septic and septic femoral venous blood were infused into a cannulated branch of the intact non-septic leg femoral artery while flow and systemic perfusion pressure were measured continuously in this leg (Fig. 2). This procedure was carried out in 13 different animals, nine of which had undergone systemic studies before and after sepsis. Ten of these experiments were successful and are summarized in (Fig. 3). In this preparation, mean femoral blood flow in the test limb (when infusing 40 ml./min. of non-septic femoral venous blood) averaged about 100 ml./min. and upon switching to septic femoral venous blood, mean femoral blood flow regularly increased to 185 ml./min. Similarly, hemoglobin saturation of the femoral venous blood draining this test leg increased and decreased, respectively, when septic and non-septic femoral venous blood were alternated. In essence, the non-septic limb assumed the hemodynamic characteristics of the septic leg when septic femoral venous blood was infused into its femoral artery. This response was not due to the vasodilating effects of hypoxia since non-

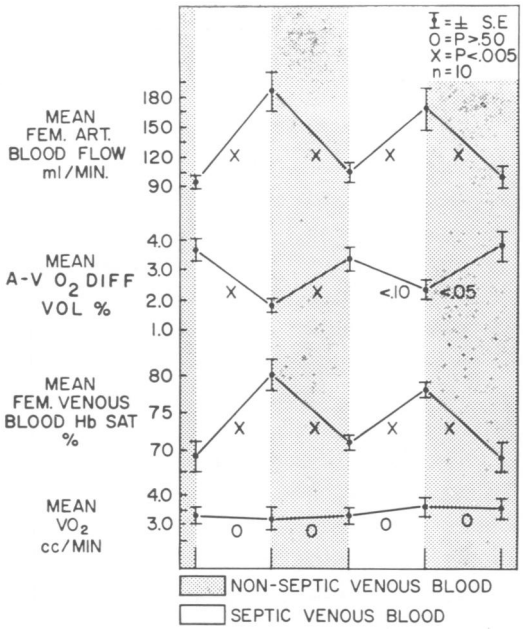

FIG. 3. Effects of alternating non-septic venous with septic venous blood at 20-minute intervals on mean femoral artery blood flow, A-V O_2 difference, femoral venous blood hemoglobin saturation and oxygen consumption in the intact contralateral hind limb in 10 experiments.

septic venous blood had the lower hemoglobin saturation and did not significantly alter blood flow. No significant change was noted in oxygen consumption of the test leg.

Figure 4 shows the change in blood flow upon altering infusions in a typical individual experiment. Femoral blood flow gradually increased from 85 ml./min. to 165 ml./min. after 20 minutes of infusing septic venous blood. A more rapid return to control level blood flow occurred after switching from septic venous blood to non-septic venous blood. Figure 5 summarizes the changes in femoral blood flow, oxygen consumption, A-V O_2 difference and femoral venous hemoglobin saturation upon changing infusions in another individual experiment. Of particular importance is the lack of change in systemic blood pressure during this procedure to account for the change in blood flow through the test leg.

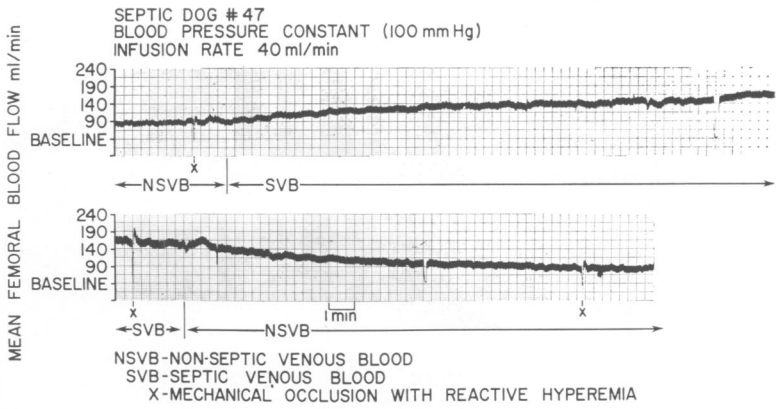

FIG. 4. A typical vascular response in the intact contralateral leg model upon alternating non-septic with septic venous blood.

Of these 13 experiments, one animal failed to respond by changing femoral blood flow when non-septic and septic blood were alternated as infusions. Another two animals responded feebly and were not included in the 10 reported experiments.

(b) *Demonstration of a Vasodilator Substance Using the Isolated Perfused Leg:* To eliminate the effects of neural influence and chronic sepsis, an isolated leg from a small, healthy puppy was perfused alternately with 25 ml./min. of arterial, non-septic and septic femoral venous blood. Flow was held constant, therefore, any change in perfusion pressure reflects a change in vascular resistance.

This procedure was carried out in seven animals, three of which responded adequately with a fall in perfusion pressure upon switching from non-septic to septic femoral venous blood. Figure 6 shows the change in perfusion pressure and oxygen consumption in the isolated leg when alternating 25 ml./min. of arterial, non-septic and septic femoral venous blood with differing hemoglobin saturation as perfusate in an individual experiment. Mean perfusion pressure was highest when arterial blood was used as perfusate. However, septic venous blood decreased perfusion pressure considerably more than non-septic venous blood even though the percentage hemoglobin saturation was higher in sep-

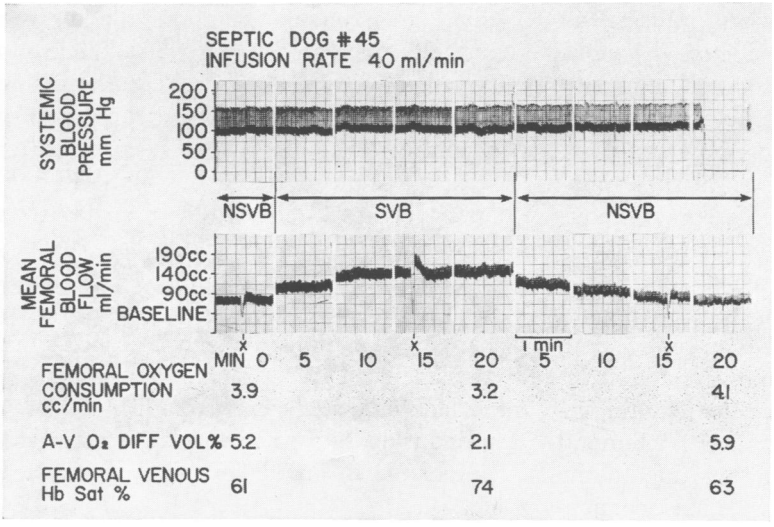

FIG. 5. A typical experiment showing the effects of non-septic (NSVB) and septic venous blood (SVB) on mean femoral blood flow, oxygen consumption, A-V O_2 difference and femoral venous hemoglobin saturation in the intact contralateral leg model. Note that no significant change in perfusion pressure occurred when non-septic venous blood was alternated with septic venous blood. Mechanical occlusion is denoted by X.

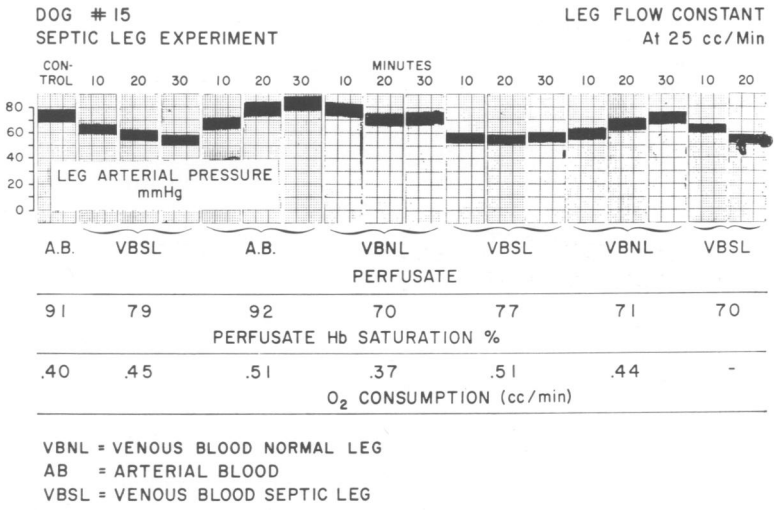

FIG. 6. The effects of using arterial blood and venous blood from the septic and opposite normal hind leg as perfusate on perfusion pressure and oxygen consumption in an individual experiment using the isolated perfused hind limb model.

tic versus non-septic venous blood. Oxygen consumption remained relatively constant with the different perfusates (Fig. 6). The four non-responding isolated perfused limbs always showed a drop in perfusion pressure when arterial blood was altered with septic femoral venous blood. Failure to elicit a response occurred when non-septic femoral venous blood hemoglobin saturation was less than 60% and septic femoral venous blood saturation greater than 75%.

These results show clearly that a vasodilator substance is present in septic venous blood that is capable of causing vasodilation in tissues beyond the septic region. It seems likely that this substance, when present in arterial blood, can profoundly alter vascular resistance and may be the primary initiating factor in the circulatory response to sepsis.

5. Nature of the Vasodilator Substance

Bacteria, endotoxins, and endogenous leukocyte pyrogens are known to exert profound direct or indirect effects on the systemic circulation. The subsequent experiments are designed to clarify the nature of the vasodilator substance we have encountered in sepsis.

(a) *Dose-Response Relationships:* In three animals, varying amounts (10 to 50 cc./min.) of septic leg venous blood were infused for 10-minute intervals into the femoral artery of the non-septic leg using the technic illustrated in (Fig. 2), to see if the response to this vasodilator is dose related. Non-septic leg venous blood was used for control. Figure 7 is a plot of these three experiments where the response (femoral blood flow in ml./min.) is represented on the ordinate and dosage (ml./min. of septic leg of non-septic venous blood) is represented on the abscissa. It appears that the response is clearly related to the dose or amount of septic blood infused into the femoral vascular bed of the non-septic leg. It should be noted that the maximal vascular response to septic venous blood frequently requires 20 minutes (Fig. 4), whereas, only 10 minutes were allowed in these studies.

(b) *Endotoxin:* The possibility that the vasodilator response in the test leg models was due to endotoxin or viable bacteria is considered in the following studies.

Six septic animals previously studied were utilized to test the local effects of endotoxin on femoral blood flow. In four animals, 100 mg. of Difco laboratory *E. coli* endotoxin was dissolved in 50 ml. of sterile

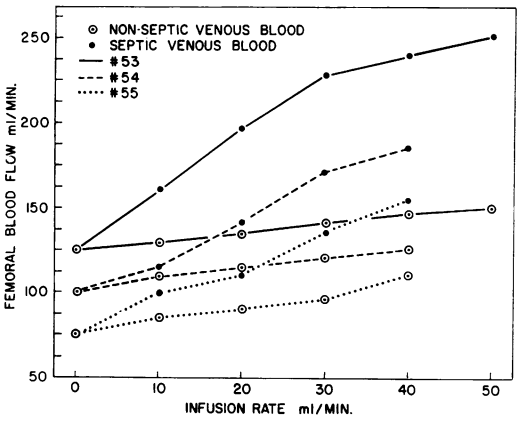

FIG. 7. The effect of altering dose (infusion rate of non-septic and septic venous blood) on the response (change in femoral blood flow) in the intact contralateral leg model in three separate experiments.

normal saline. With a Harvard infusion pump, concentrations varying from 0.1 mg./min. to 20 mg./min. were infused locally into the femoral artery of 20–25 Kg. animals. Starting with the lowest concentration, the infusion rate was gradually increased at 3-minute intervals to progressively higher concentrations. No change in local femoral blood flow was noted with this technic. Systemic blood pressure, however, uniformly decreased in all experiments after 50–75 mg. of the endotoxin had been administered. In two animals, endotoxin was given as a bolus of 0.25, 0.5, 1.0, 2.0 and 4.0 mg. locally into the femoral artery. A temporary increase in femoral blood flow was noted with all doses, but this response soon became damped suggesting tachyphylaxis. In addition, systemic blood pressure rapidly decreased with endotoxin. In contrast, the septic venous blood vasodilator substance increased blood flow to a greater degree and did not change systemic blood pressure.

(c) *Bacteria:* Four animals previously studied were used to study the effects of free bacteria infused locally on femoral blood flow. *E. coli* isolated from human urine and grown on tryptic soy agar slants for 24 hours were prepared according to the technic employed by Hinshaw *et al.*[19] In brief, a suspension of viable washed organism ranging in concentration from 1×10^7 to 1×10^{10} organisms/ml. normal saline were obtained. Aliquots of this suspension ranging from 0.10 to 3.2 ml. were then injected as a bolus into the non-septic leg femoral artery in two animals weighing 26 kilograms. Only transient (2–3 minutes) hyperemia (25–50 ml./min. increase in blood flow) was noted with the larger bolus of organisms (0.8, 1.6 and 3.2 ml.). Infusion of the suspension of organisms with a Harvard infusion pump ranging in amounts from 0.10 to 10 ml./min. was without effect on local femoral blood flow in the other two animals weighing 23 kilograms.

(d) *pH, P_{CO_2}, Potassium, Temperature, Hb Sat., Lactate:* All of the above have been shown to alter the tone of resistance vessel smooth muscle. In our studies, no significant differences were noted between non-septic and septic leg venous blood P_{CO_2}, temperature, potassium and pH. However, septic leg venous blood had an average hemoglobin saturation of 81%, whereas, non-septic venous blood hemoglobin saturation averaged 69% (Table 3). Lactate, likewise, was slightly elevated in septic leg venous blood (0.47 mM./l.) over that observed (0.37 mM./l.) in the non-septic leg venous blood (Table 3).

(e) *Response of Septic Tissue to Pharmacological Agents:* Various vasoactive agents such as plasma kinins, histamine and serotonin have been found to be present in increased quantities in inflamed tissue[26] and may be responsible for the increased blood flow through the septic region. It is assumed that the vasodilator demonstrated in these studies exists in septic tissue and also influences the tone of the resistance vessels in this region. A clue to the nature of this vasodilator substance was sought by infusing various pharmacological agents locally into the septic vascular bed and observing the response to these substances. To do this, a flow probe was

attached to the septic leg femoral artery and various pharmacological agents were administered locally in doses which failed to produce systemic effects.

Table 6 summarizes the various agents used, the doses administered and the vascular response reported as per cent change from control blood flow with these drugs in six animals. Blood pressure remained constant throughout these studies and, therefore, an increase or decrease in blood flow denotes a corresponding inverse change in vascular resistance.

The septic vascular bed responds qualitatively to numerous pharmacological agents in the same manner as a non-septic hind limb with one exception. Phenoxybenzamine fails to alter blood flow through the septic hind leg, whereas, vasodilation normally occurs in the contralateral non-septic leg after local administration of this drug. Although the above qualitative data does not rule out any of the mentioned agents as mediators of the circulatory response observed in sepsis and locally in the septic region, one would expect some change in vascular response with antagonist or stimulants if large quantities of any of these substances were present in septic tissue.

TABLE 6. *Vascular Response of the Septic Leg to Various Pharmacological Agents*

Pharmacological Agent	Antagonist	Blood Flow (% change)
Histamine sulfate (5 μg./min.)		↑ 25–50
	Diphenhydramine HCl (200 μg./min.)	N.C.
Bradykinin (100–200 ng./min.)		↑ 25–50
	Carboxypeptidase B (20–40 mg./min.)	N.C.
Serotonin (2μg./min.)		↓ 25–50
	Lysergic acid (25 μg./min.)	N.C.
Phenylephrine (4 μg./min.)		↓ 25–50
Norepinephrine (1 μg./min.)		↓ 50–75
Epinephrine (1 μg./min.)		↓ 50–75
	Phenoxybenzamine (5–10 mg./min.)	N.C.
Isoproterenol (0.2 μg./min.)		↑ 25–50
	Propranolol (2 mg./min.)	N.C.
Acetyl choline (2 μg./min.)		↑ 25–50
	Atropine (0.25 mg./min.)	N.C.
Angiotensin (0.2 μg./min.)		↓ 25–50
Nitroglycerin (0.03 mg./min.)		↑ 25–50

N.C. = No change.

6. Non-responding Animals

Clowes [1, 8] has observed that those patients and laboratory animals who fail to increase their cardiac output with sepsis usually expire from their illness. The basis for this lack of responsiveness is still unclear. As in Clowes' studies, we have found that about 20% of our animals fail to increase their cardiac output. Whether these non-responding animals in our studies would have expired is unknown since they were sacrificed after 48–72 hours of sepsis.

Four of the original 24 animals which underwent studies before and after sepsis were eliminated from this study for the following reasons: 1 died following sepsis, another developed a large pulmonary abscess, and two animals had control cardiac indices above 5 l./min./m.^{2} It should be noted, however, that the latter three animals all increased their cardiac output with sepsis. Five animals of the original 24 failed to respond by increasing their cardiac output in response to sepsis (Table 7). Two of these animals developed only

TABLE 7. *Effects of Sepsis on 5 Non-responding Animals*

Measurements and Calculations	Control (mean ± S.E.)	*P* Value	Sepsis (mean ± S.E.)
Cardiac index (l./min./m.^{2})	3.7 ± 0.2	N.S.	3.3 ± 0.2
Arterial blood pressure (mm.Hg)	122 ± 10	N.S.	104 ± 5
Total peripheral vascular resistance index (mm. Hg/l./min./m.^{2})	34 ± 4	N.S.	32 ± 1
Arterial hematocrit (%)	38 ± 2	N.S.	37 ± 3
Pulse rate (beats/min.)	138 ± 9	N.S.	154 ± 2
Rectal temperature (°C.)	38.4 ± 0.2	<0.001	39.3 ± 0.4
Systemic oxygen consumption (cc./min./m.^{2})	161 ± 10	N.S.	165 ± 8
Arterial pH	7.37 ± 0.02	N.S.	7.37 ± 0.01
Arterial Hb SAT (%)	92 ± 1	N.S.	92 ± 1
Arterial P_{CO_2} (mm.Hg)	38 ± 1	<0.025	32 ± 2
Plasma HCO_3^- (mM./l.)	21 ± 1	<0.05	18 ± 1
Arterial blood lactate (3) (mM./l.)	0.38 ± 0.03	N.S.	0.37 ± 0.02
Arterial blood pyruvate (3) (mM./l.)	0.035 ± 0.001	N.S.	0.036 ± 0.002
Femoral artery blood flow (ml./min.)	181 ± 24	†<0.01 *<0.10	96 ± 5 263 ± 43
Femoral vascular resistance (mm.Hg/ml./min.)	0.67 ± 0.13	†<0.025 *<0.05	1.06 ± 0.04 0.43 ± 0.06
Femoral venous Hb SAT (%)	81 ± 3	†<0.05 * N.S.	73 ± 2 83 ± 2
Femoral oxygen consumption (cc./min.)	3.4 ± 0.5	† N.S. * N.S.	3.0 ± 0.3 4.6 ± 0.7
Femoral venous blood lactate (3) (mM./l.)	0.37 ± 0.04	† N.S. * N.S.	0.39 ± 0.04 0.45 ± 0.03
Femoral venous blood pyruvate (3) (mM./l.)	0.034 ± 0.001	† N.S. * N.S.	0.035 ± 0.002 0.039 ± 0.005

( ) Number of animals other than 5.
* Septic leg.
† Non-septic leg.

mildly septic legs and this may account for their non-responsiveness. The other three animals had full blown septic legs but failed to respond by increasing their cardiac output. Table 7 summarizes the response of these five dogs.

Discussion

Clowes [8] has shown that sepsis in man frequently induces a hyperdynamic cardiovascular response characterized by tachycardia, hypotension, high cardiac output and low total peripheral vascular resistance. Our early studies showed clearly that this response is evident even in the unique hemodynamic pattern of septic shock.[27] These measurements in clinical sepsis and septic shock have created dissatisfaction with the canine endotoxin shock model where the low cardiac output and intense vasoconstriction in no way mimics the naturally occurring condition in humans.

Several mechanisms must now be considered in explaining the heightened circulatory requirements in sepsis; increased metabolic demands with sepsis and pyrexia, altered vasomotor center activity due to the primary effects of septic products on this region or due to altered baroceptor firing in the face of generalized or localized vasodilation with hypotension.

Kinney and Roe [20, 24] have measured the metabolic requirements in sepsis and other states and have stressed that many factors other than fever play a major role in caloric expenditure. Our studies clearly show a disproportionate increase in cardiac output in relation to the metabolic needs of the organism in sepsis and suggest that the heightened cardiac output is mediated largely by factors other than increased energy requirements.

Albrecht and Clowes [1] state that blood flow is "considerably increased" through the inflamed region. Our studies confirm and quantitate this observation. However, their suggestion that this area may accommodate a large portion of the extra cardiac output is not borne out by our measurements since only approximately 10% of the extra cardiac output is accommodated by the septic region. Our present studies clearly show that increased blood flow through the septic area cannot, in itself, account for the extra cardiac output seen in sepsis.

The concept of arterio-venous shunting implies non-nutritional flow and to be a dominant route in the microcirculation, evidence of cellular hypoxia must be demonstrated. Excessive lactate production (A-V lactate difference × blood flow) was not noted across the septic vascular bed in our studies and oxygen consumption actually increased in the inflamed region indicating that vasodilation rather than perfusion of non-nutrient vessels predominated.

The increased cardiac output seen in sepsis is diverted to the kidneys, splanchnic organs and septic region. A vasodilator substance continuously released from the area of sepsis appears to account for this phenomenon. Since this substance follows a dose-response relationship, one would expect those vascular beds normally receiving the highest blood flow to be influenced to a greater degree than tissues with less abundant blood flow such as skeletal muscle at rest. Relative hypotension acting by way of the baroceptors would bring about a reflex hyperdynamic cardiac drive and an attempt at vasoconstriction to maintain blood pressure. The seemingly paradoxical situation of vasoconstriction in the non-septic hind limb (which probably reflects vasoconstriction in skeletal muscle and skin in general), in the face of vasodilation in the core organs can be explained readily. Whether a given vascular bed will be dilated or constricted will depend upon a balance between sympathetic vascular tone and the influence of the vasodilator substance on vascular smooth muscle. Sympathetic vascular tone is high in skeletal muscle [3] and overpowers the influence of the vasodilator substance. However, sympathetic vascular tone in the kidneys and splanchnic organs is insufficient to abrogate the influence of large amounts of the vasodilator substance reaching these organs. Clearly, these studies show that regional blood flow in this model is determined by the balance of these two factors since the vasoconstricted non-septic leg becomes dilated when extra septic venous blood reaches it (Fig. 3) and conversely, the vasodilated septic limb vasoconstricts when exposed to norepinephrine (Table 6).

An alternate explanation to account for the differences in responsiveness of skeletal muscle versus the kidneys and splanchnic organs to the vasodilator substance observed in our studies stems from the work of McNay *et al.*[22] on dopamine. It has been suggested that dopamine receptors exist in renal and splanchnic organs in contrast

to skeletal muscle and may account for the different vascular responsiveness of these organs to various pharmacologic agents and endogenously occurring substances.[29]

The nature of this vasodilator substance is unclear. Preliminary qualitative studies fail to implicate plasma kinins or histamine, nor can the local vasodilation in the test limb preparations be duplicated by acute local administration of endotoxin or free bacteria.

Numerous exogenous substances such as bacteria, viruses, injured, foreign, or necrotic tissue and antigens from non-animal origin have been shown to elicit a pyrogenic response in man and animal.[10, 28] In general, it is believed that these exogenous materials induce fever by way of an endogenous pyrogen released from the polymorphonuclear leukocyte,[10] monocytes [2, 4] and perhaps other cellular elements of the body.[18] The site of action of these endogenous pyrogens in inducing pyrexia is disputed.[7, 18, 23]

Less well studied are the circulatory effects of sub-lethal amounts of pyrogenic substances.[12] Homer Smith [5, 25] and other early renal physiologists have observed that inulin contaminated with bacterial products induces pronounced renal hyperemia and an increase in cardiac output after a latent period of 40–80 minutes, presumably, by way of endogenous pyrogens. Bradley and Conan [6] have observed that estimated hepatic blood flow increases significantly upon administration of bacterial products again after a latent period of 40–80 minutes. These circulatory responses do not appear to be dependent upon the febrile response since administration of antipyretic agents which are effective in abolishing the febrile response have little effect on the increased cardiac output and renal hyperemia.[5, 25]

The site of action of exogenous pyrogenic materials in mediating this circulatory response is unclear. These circulatory effects are very likely mediated by way of endogenous pyrogens since there is a latent period before the full circulatory response is noted that is comparable to that seen with a pyrogenic reaction.[15] Cooper *et al.*[11] have suggested that the renal hyperemia observed after administration of these exogenous pyrogenic substances is mediated by a humoral agent (perhaps the endogenous pyrogens) since renal hyperemia is still seen after sympathectomy and also in the transplanted kidney.

The observation made by Smith,[25] Bradley [5, 6] and others [14, 16] that exogenous pyrogenic substances increase cardiac output, renal and splanchnic blood flow correlate well with the findings observed in our experimental septic model. It would appear that with prolonged sepsis, an abundant and continuous supply of this endogenous pyrogen is produced from the bacterial-host tissue interaction in the septic region and released into the systemic circulation.

The importance of the high circulatory requirements in sepsis is evident under circumstances where the metabolic demands are already high in cases of burns and other injuries. Cardiac failure in sepsis and septic shock is now a recognized complication and may be explained by the inability of the heart to maintain the high cardiac output necessary to sustain blood pressure in the face of vasodilation. Finally, this tenuous state of the circulation may account for the brittle behavior of these septic patients who are readily tipped into shock or cardiac arrest when additional metabolic or circulatory demands are added.

Summary

Creation of a septic leg in dogs increased the cardiac index 50% (1,600 ml./min.), systemic oxygen consumption 12%, the rectal temperature 1.3 centigrade degrees, pulse rate 24% and decreased mean blood pressure 16% and total peripheral vascular resistance 46%.

Significant re-distribution of blood flow away from non-septic skeletal muscle (39% decrease) to splanchnic organs (38% increase), kidneys (60% increase) and the septic region (81% increase) occurred.

A powerful vasodilator (possibly an endogenous pyrogen resulting from bacterial-host tissue interaction) is released from the septic region which has the potential to cause vasodilation in regions beyond the septic area. It is hypothesized that this vasodilator substance is primarily responsible for the circulatory response to sepsis.

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Discussion

Dr. George Clowes (Boston): We have heard a fine paper. It has helped to explain a number of the observations dealing with the problem of what kills the septic patient, in particular the presence of the excessively high cardiac outputs which are often poorly tolerated by the damaged myocardium.

To demonstrate the validity of these experimental observations, in terms of the clinical problem in man, I would like to compare for you two series of patients in whom we have examined the circulatory and metabolic responses. [Slide] A series of patients who recovered uneventfully from major surgical operations exhibited relatively normal cardiac outputs and peripheral vascular resistances in the postoperative period. They had little or no excess lactate during their convalescence, and the metabolic rate was elevated but 8 per cent.

[Slide] In this slide we compare the data from normal convalescence with those from this unfortunate but typical patient who developed peritonitis due to a leaking gastroenterostomy. During the stable periods, when he was obviously doing satisfactorily, he had very high cardiac outputs, more than twice his normal resting value. At the same time, though, he ran rather large excess lactate values, suggesting that in spite of these high cardiac outputs, he was not satisfying the circulatory demands of his tissues. The other thing I would point out is that his metabolic rate did not rise proportionately to the cardiac index, just as it did not in the dogs that we have heard about. From 1900 calories per day, it merely rose to 2300.

[Slide] Summarizing the data from 78 patients, I would point out that the average cardiac index was 3 liters for the patients who were making uneventful recovery and about 4.5 in the septic patients that were in a steady state. The important point is that the elevation of the metabolic rate was only 37 per cent as compared with an increase of 57 per cent in the cardiac output. Those patients who could not maintain this high cardiac output were the ones who died.

When we search for causes for the marked reduction of peripheral vascular resistance, we must consider the normal circulatory requirements caused by higher body temperature and increased work of respiration. However, we must consider also the abnormal peripheral shunts that have been demonstrated to you in the inflammatory region. In addition I would like to bring to your consideration one more thought as to why we may have an extra circulatory demand manifested by reduced vascular resistance in other tissues.

Look at the excess lactate values. 0.5 mM/L is average in the patients making uneventful convalescence, whereas the people who were septic, even the ones doing well with high cardiac outputs, had 1.4 millimols per liter. Those in the preterminal group exhibited even higher values, averaging 2.2 mM/L.

In addition to the presence of circulating vasodilator peptides suggested by the authors as a reason for the reduced peripheral vascular resistance, one might postulate a reduction of arteriolar contractility due to the accumulation of metabolites. In this regard the high lactate values in the septic people who were doing well suggests that possibly three things could be happening: 1) Capillaries could be plugged, or arterioles plugged, with microthrombi; 2) An increase of interstitial edema, as occurs in the lung could be blocking diffusion of oxygen. Either situation should result in anaerobic glycolysis; and 3) An intrinsic metabolic abnormality of cellular metabolism might well be producing metabolites.

The fact remains that regardless of its origin the presence of this excess lactic acid or other metabolites may be very strong stimuli for the dilation of vessels which are still functioning in many tissues outside the inflammatory area. Herein may be an explanation for the huge demand for circulation which usually far exceeds the increase of the metabolic rate.

Dr. John Martin Kinney (New York): There are two particular points on which we have information which is somewhat parallel in man to the data reported here in the animal.

Drs. Hermreck and Thal found that the amount of fever in the animals who responded to the leg infection had a rise in cardiac output of over 20 per cent and those that did not was surprisingly similar. The nonresponders were in a situation in which they had very little increase in oxygen consumption.

In an extensive clinical study which was reported several years ago, we were surprised to find very similar findings. Namely, that fever is a very poor factor on which to predict whether there is an increase in oxygen consumption and apparently is also poor to predict an increase in the cardiac output itself.