TRANSVASCULAR FLUID MOVEMENT AND SEGMENTAL VASCULAR RESISTANCES IN RESPONSE TO TRANSFUSION IN ENDOTOXIN SHOCK

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ABSTRACT

TRANSVASCULAR FLUID MOVEMENT AND SEGMENTAL VASCULAR RESISTANCES IN RESPONSE TO TRANSFUSION IN ENDOTOXIN SHOCK

By

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The aim of this study was to determine if transfusion leads to fluid filtration and a disproportionate rise in extravascular fluid volume (EFV) in dogs previously injected with endotoxin relative to that seen in saline controls. Male mongrel dogs were anesthetized with sodium pentobarbital and injected with either purified E. coli endotoxin (5 mg/Kg, i.v.) or saline, and after 2 hours were transfused with 1000 ml of cross-matched whole blood over a period of 25 min. There was no change in forelimb weight, segmental vascular resistances, blood flows or blood pressures in the saline dogs prior to transfusion. Following transfusion forelimb weight increased markedly relative to control (22 g in 2 hrs). The weight gain occurred concurrently with significant increases in right atrial pressure (which would indicate an increased capillary hydrostatic pressure in an intact animal), aortic pressure, small vein pressures, and hematocrit and with no change in segmental vascular resistances. Hence,

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W. Jeffrey Weidner

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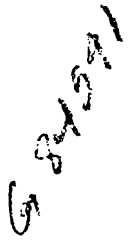

DEDICATION

This one is for Saint Alia of-the-Knife and Duncan Idaho, the sleeping dogs, and all the long necked bottles.

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CHAPTER 1

INTRODUCTION

A significant percentage of circulatory shock cases resulting from endotoxin become refractory to treatment, i.e., blood volume restoration with or without additional pharmacological therapy (37, 47). For this reason endotoxin shock is clinically associated with a high mortality rate. A serious obstacle to the successful treatment of this condition is the lack of complete data on its pathophysiology. This study is an attempt to provide further definitive information on one aspect of endotoxin shock, namely, the role of transcapillary fluid fluxes in skin and skeletal muscle in determining irreversibility after transfusion.

Transvascular fluid efflux, especially into skeletal muscle, has been suggested as a possible determinant of irreversibility in endotoxin shock since it is thought to lead to loss of plasma volume and subsequent decline in total blood volume. The literature on this subject, however, is inconsistent with respect to the site and magnitude of such fluid fluxes. Several factors may account for these conflicting observations: species variation in response to endotoxin; error associated with plasma volume measurements

made with dilutional techniques, particularly in vasoconstricted states since adequate mixing of the dye may not occur; the inability of dilutional techniques to separate measured decreases in blood volume due to fluid efflux from decreases due to intravascular pooling. Moreover, aside from a previous study by Weidner et al., transcapillary fluid fluxes in skeletal muscle have not been studied specifically, but alleged fluid efflux has been inferred from changes in hematocrit and plasma volume (61). In the previously mentioned study, which utilized a gravimetric technique, no evidence was found for fluid filtration during the hypotensive period in dogs subjected to endotoxin shock; in fact, only evidence for extravascular fluid reabsorption from skin and skeletal muscle was found (61). Similar findings have been reported by Hinshaw and Owen utilizing a canine forelimb preparation (30). This phenomenon may not occur following transfusion, however, since the hemodynamic relationships change markedly. Blood volume restoration increases vascular pressures, under these conditions changes in the precapillary to postcapillary resistance ratio and/or microvascular membrane permeability to plasma proteins have a quantitatively greater effect on both the direction and rate of transvascular fluid fluxes than similar changes in these variables when vascular pressures are low. Thus, it is important that the prolonged

effect of transfusion be critically examined to determine if net fluid efflux into skin and skeletal muscle occurs in animals subjected to endotoxin shock.

In an attempt to circumvent some of the problems encountered with dilutional techniques, such as inadequate mixing of dyes, endotoxin shock has been studied utilizing a gravimetric technique. Transcapillary fluid fluxes in the canine forelimb were estimated from changes in forelimb weight and segmental vascular resistances. The forelimb has been selected as the test organ since it is largely composed of skin and skeletal muscle.

CHAPTER II

REVIEW OF LITERATURE

Endotoxin shock, often called bacteremic or septic shock, is a condition resulting from the liberation of a lipoprotein-carbohydrate complex from the cell wall of certain gram negative bacteria, of which E. coli is an example. Endotoxin, once it enters the vascular system of an animal, has pronounced deleterious effects and is often fatal. Although the response to endotoxin is not the same in all species, hypotension is common to all.

Canine endotoxin shock following i.v. injection of purified endotoxin is generally associated with the following responses: systemic arterial pressure (SAP) falls abruptly within 2-5 minutes, transiently recovers toward control levels (min. 20-45), and then gradually falls unto death (3); right atrial pressure (RAP) falls within 1-3 minutes and remains below control (3, 51, 56); cardiac output (CO) falls precipitously within 2-5 minutes and follows a pattern similar to SAP (3, 54); calculated plasma volume (PV) has been reported to progressively decrease up to 36% (3); after an initial brachycardia, heart rate

remains elevated above control (3); no significant change in myocardial contractility occurs until the terminal stages (3, 4, 51). Total peripheral resistance (TPR) increases markedly within 2-5 minutes following endotoxin administration, wanes (min. 20-45) and then either increases from 60 minutes until death or further decreases (until min. 120-180) before increasing until death (3). Hematocrit, after an initial decrease (0-10 min.), has been reported to rise continuously (3, 4).

Decreased flow, subsequent to a decreased blood volume resulting from vascular pooling and/or from transvascular fluid loss is thought to be the major determinant of irreversible shock from endotoxin in the dog (3, 25, 34, 56, 57). Endotoxin administration into live animals elicits a number of responses which are known to affect transcapillary water movement across capillaries and the intravascular distribution of blood. Transcapillary water movement is regulated by the transmural hydrostatic pressure gradient and by the transmural colloid osmotic pressure gradient. Capillary hydrostatic pressure (Pc) is an important determinant of the former; a rise in this variable (as occurs with transfusion) above colloid osmotic pressure (COP) promotes fluid efflux, while decreased capillary hydrostatic pressure (as occurs with hemorrhage) below COP facilitates fluid influx (46). Capillary hydrostatic pressure is determined by the compliance of the capillary wall and capillary blood

volume. Capillary blood volume is determined by the precapillary to postcapillary resistance ratio and by aortic pressure and right atrial pressure. Resistance in the precapillary and postcapillary segments is related to vessel caliber and blood viscosity. Vessel caliber is a function of changes in vascular smooth muscle (active changes) and changes in transmural pressure independent of changes in smooth muscle activity (passive changes). A decrease in systemic arterial pressure, right atrial pressure, or postcapillary resistance, or increase in precapillary resistance will tend to lower capillary hydrostatic pressure. Likewise an increase in systemic arterial pressure, right atrial pressure, or postcapillary resistance, or a decrease in precapillary resistance will tend to produce the opposite effect on capillary hydrostatic pressure. The transmural colloid osmotic pressure gradient can be altered by a change in microvascular permeability to plasma proteins as well as by abnormal lymph drainage.

Endotoxin shock is associated with altered net fluid fluxes across the capillaries. Net fluid influx is believed to occur initially. Measurements of hematocrit and plasma protein concentration are compatible with the early influx of fluid in that both decrease initially in the intact dog (3, 4, 28). In splenectomized dogs similar changes are seen in hematocrit and plasma protein concentration; also plasma

volume (PV) reportedly increases (3, 4, 58). In primates, including man, plasma volume increases; hematocrit and plasma protein concentration decrease (3, 21, 56). This also suggests that the early stage of endotoxin shock is associated with extravascular fluid reabsorption. The initial fluid influx following endotoxin injection has been attributed to a fall in capillary hydrostatic pressure, especially in skeletal muscle (3, 4, 61). Capillary hydrostatic pressure is thought to fall subsequent to the fall in systemic arterial pressure and right atrial pressure and an increased precapillary to postcapillary resistance ratio (9, 19, 21, 26, 34). The initial fluid influx is viewed as an important compensatory mechanism, which serves to increase blood volume (9, 21). An increased blood volume would serve to increase venous return and subsequently cardiac output.

The direction of net fluid movement has been reported to reverse with time (45-60 minutes after endotoxin administration) due to increased capillary hydrostatic pressure and/or increased microvascular permeability to proteins (3, 4, 33, 37). This is viewed by some authors as important in the development of irreversibility since it serves to critically reduce both the effective blood volume and total blood volume. A decreased total blood volume leads to decreased venous return and subsequently to decreased cardiac output. In dogs a continuous rise in

hematocrit and plasma protein concentration has been observed after the initial decrease (3, 4, 53). Weight continuously increases in forelimbs perfused at constant flow (24). This has been interpreted as evidence for a net fluid efflux (34, 50). However, under conditions of constant flow, weight increases may occur subsequent to increased capillary hydrostatic pressure due to venoconstriction. And, although compatible with plasma volume loss, does not necessarily mean plasma volume loss occurs at natural flow. In this regard recent experiments by the author are important (61). An isolated forelimb preparation was used to investigate transvascular fluid fluxes in dogs subjected to endotoxin shock. Forelimb weight fell throughout a four-hour period. The weight loss was associated with a fall in total forelimb resistance from minute 10 throughout the remainder of the observation period. The fall in forelimb resistance suggests that mean blood vessel caliber and forelimb intravascular blood volume were increasing during this period. A sustained weight loss accompanied by an increasing intravascular blood volume must be attributed to extravascular fluid reabsorption. Like findings have been reported recently by other investigators (30). This data is not inconsistent with an endotoxin induced increase in microvascular permeability to plasma proteins, however if microvascular permeability did increase, the

increase was insufficient to promote net fluid efflux and extravascular fluid reabsorption continued. These data fail to provide evidence for fluid filtration into skin and skeletal muscle during prolonged endotoxin hypotension, but support the concept that endotoxin hypotension is accompanied by extravascular fluid reabsorption. Dogs also develop diarrhea, which demonstrates that some fluid is lost into the intestinal lumen. The volume of fluid lost through the intestine is relatively small and is not enough in itself to cause irreversibility (20). Intestinal necrosis and bloody diarrhea do not occur in cats or primates (27, 36, 58).

The intravascular distribution of blood is affected by factors that affect vascular capacity. Vascular capacity is affected by changes in vessel compliance and by active and passive changes in vessel caliber. Reported losses in plasma volume in both the early and late stages of endotoxin shock are frequently attributed by some authors to extensive fluid efflux. These losses, however, may be due wholly or in part to vascular pooling of blood. Peculiar to the canine species during the early stage of endotoxin shock is an hepatic venoconstriction occurring within 1-2 minutes after administering endotoxin. This venoconstriction decreases in intensity at 3 minutes and essentially disappears within 20 minutes. It is responsible for the initial rise in capillary hydrostatic pressure in the hepatosplanchnic

vascular beds, and has been implicated as the cause of impeded venous return which serves to precipitate the early hypotensive phase of endotoxin shock in the dog (3, 24, 27, 29, 35, 38, 40, 53). This venoconstriction is reported to be responsible for vascular pooling of blood in the hepatosplanchnic beds during the early phase of endotoxin shock (12, 20, 29, 38). Increases of up to 35 g/100 g tissue weight occur in the small intestine (20). Liver weight increases from 80 to 350 g have been reported to occur within 3 minutes following endotoxin. This response is short-lived, however, since weight returns to control within 30 minutes (38). In the late stage of endotoxin shock little or no evidence exists for vascular pooling in the hepatosplanchnic beds or other organs.

During endotoxin shock, systemic arterial and right atrial pressures decrease appreciably while peripheral precapillary resistance increases. This would tend to lower capillary hydrostatic pressure. In order for capillary hydrostatic pressure to increase under these conditions, post capillary resistance would have to rise markedly to overcome the effects of the fall in systemic arterial and right atrial pressures and the increase in precapillary resistance. If the rise in postcapillary resistance were of sufficient magnitude, a rise in capillary hydrostatic pressure above colloid osmotic pressure would promote fluid efflux. This is unlikely considering the hemodynamics of

the shock state. After endotoxin administration systemic arterial pressure frequently falls to 30-40 mm Hg and right atrial pressure is frequently 0 mm Hg or less. If in this case, the precapillary to postcapillary resistance ratio fell from a control of 4 to as low as 1, calculated capillary hydrostatic pressure would be between 15 and 20 mm Hg, well below colloid osmotic pressure (see Appendix for calculation). It is thus unlikely that extravasation of fluid takes place during extreme hypotension unless capillary membrane permeability to plasma proteins is substantially increased. This agrees with the author's previously published findings for prolonged endotoxin induced hypotension in which only evidence for extravascular fluid reabsorption from the forelimb was found (61). However, this may not be true following transfusion. In dogs subjected to endotoxin shock, transfusion of either whole blood or dextran significantly increases blood pressure (2, 43). Cardiac output is increased significantly, but may begin to fall after a variable period of time, usually 3 to 6 hours after transfusion (2). Central venous pressure increases significantly after transfusion, but also may fall after a variable period of time (2). Hematocrit is significantly lowered in response to transfusion with low molecular weight dextran (59). pH falls significantly less in dogs subjected to transfusion after endotoxin administration than in dogs given endotoxin

alone (2, 59). The marked rise in central venous pressure, which is associated with increased cardiac output, diminished transit time and diminished peripheral resistance suggests an increased venous return (1, 2). Transfusion following endotoxin shock also improves certain parameters in primates. Infusion of either blood or dextran reportedly increases cardiac output, central venous pressure, right atrial and systemic arterial pressures (5). Peripheral vascular resistance has been observed to decrease in response to transfusion, as does heart rate (5). Conflicting evidence exists, however, with respect to the effect of transfusion in primates, as both cardiac output and central blood volume have been reported to decrease in monkeys in response to transfusion following endotoxin administration (59).

Although central venous and right atrial pressures and cardiac output are elevated by fluid replacement, vascular behavior may not be beneficially affected in peripheral beds, nor it does not necessarily follow that normal conditions will be restored to the microvasculature. After transfusion, then, the hemodynamic situation is altered since transfusion increases vascular pressures. Under conditions of increased vascular pressure, changes in the precapillary to postcapillary resistance ratio and/or microvascular permeability to plasma proteins have a far greater effect on both the direction and rate of transvascular fluid fluxes than do similar changes in these

variables when the vascular pressures are low. The effects of transfusion on transvascular fluid fluxes in endotoxin shock states have yet to be investigated.

The majority of studies in the literature pertaining to the effect of transfusion during endotoxin shock are concerned with survival rate. Transfusion, either of whole blood or dextran, into both dogs and primates, including humans, in endotoxin shock is known to markedly increase survival time, but often does not alter ultimate hemodynamic deterioration (49, 51).

Evidence exists which suggests that capillary membrane permeability to plasma proteins is increased during endotoxin shock (3, 50). A fall in the transmural colloid osmotic pressure gradient could promote fluid efflux even if capillary hydrostatic pressure does not increase. Since vascular pressures are increased by transfusion, fluid efflux in the face of increased microvascular permeability would tend to be of greater magnitude than that caused by increased capillary hydrostatic pressure alone. If capillary hydrostatic pressure falls, however, a decreased transmural colloid osmotic pressure gradient would not necessarily result in extravasation of fluid. Indeed, if the transmural hydrostatic pressure gradient fell proportionately more than the transmural colloid osmotic pressure gradient, filtration of fluid would not occur, but

extravascular fluid reabsorption would result. The reported decrease in measured blood volume is usually attributed to intravascular fluid loss by filtration, although it could as well be attributed to intravascular pooling of blood since, in vasoconstricted states, the indicator may not penetrate into the pooled blood and thus erroneously low plasma volume measurement occurs. In splenectomized dogs dilutionally measured plasma volume does not significantly change or may increase slightly; hematocrit and plasma protein concentration decrease, suggesting hemodilution rather than fluid loss (3, 4, 54). In primates, including man, there is likewise no evidence for a progressive plasma volume loss, measured plasma volume does not progressively decrease, nor do hematocrit or plasma protein concentrations progressively increase (8, 12, 25, 34, 58). Weight has been reported to continuously decrease for 120 minutes in response to endotoxin (1 mg/Kg) in autoperfused canine forelimbs (33). These findings are consistent with the author's previously mentioned findings. However, this may not be true following transfusion, after which hemodynamic relationships are significantly altered.

Following systemic administration of endotoxin in dogs total peripheral resistance has been reported to increase greatly within 5 minutes, wane from 20-45 minutes, and either increase from 60 minutes until death or continue

to further decrease toward control for a variable period and then increase until death (3, 35, 39). Systemic administration of endotoxin in dogs has been reported to produce an early transitory phase of increased total resistances in autoperfused splanchnic, hepatic, renal, hindlimb and forelimb vascular beds and then resistances partially wane with time (23, 29, 39, 40). The cerebral and coronary vascular beds show relatively little change in resistance in response to systemically administered endotoxin (39, 48). Systemic infusion of endotoxin also increases resistance in vascular segments which are series coupled in the autoperfused forelimb. Segmental vascular resistances in skin and skeletal muscle (large arterial, small vessel, large venous) increase abruptly within 2-5 minutes and then skeletal muscle resistances partially wane with time, while skin resistances remain elevated (33).

Local i.a. administration of endotoxin to various vascular beds has been reported to have only small transient effects on the renal, hindlimb and forelimb vascular resistances (13, 22, 34, 39). The coronary bed has been reported to show a decreased resistance when given endotoxin locally (11). However, the isolated canine liver and small intestine when perfused with endotoxin show increased resistances (29).

The observed change in total peripheral resistance in canine endotoxemia is seemingly a phenomenon due both to active and passive factors. Active changes in vessel caliber are due to indirect actions of endotoxin, since local administration apparently has little or no effect on most vascular beds (51). Indirect active changes in vessel caliber are due to neurogenic effects and to chemical factors which are liberated into the bloodstream by endotoxin (42, 44, 45). Passive decreases in vessel caliber may be precipitated by blood viscosity increases which increase vascular resistance and hence lower blood flow. These may be precipitated either directly or indirectly by endotoxin, i.e., increased hematocrit and hypercoaguability (18). Total peripheral resistance may also rise as the result of passive geometrical factors, such as decreases in vessel radius which occur as a result of a fall in transmural pressure, especially in the late stages of endotoxin shock (22). It has been shown that hepatosplanchnic resistance changes and pooling are not dependent on an intact nerve supply to the viscera or to the presence of the adrenal glands (21). Late changes in resistance are more pronounced in intact dogs than splenectomized dogs and can be related to a rise in blood viscosity resulting from splenic emptying (3, 4, 40). Monkeys, in response to endotoxin, show a decreased total peripheral resistance throughout the experimental period, as do eviscerated dogs (12, 25, 28).

The development of a progressive systemic hypotension in the dog following endotoxin administration has been explained by decreases in cardiac output (12, 26). Endotoxin has been reported to cause a lowered setting of the baroreceptors which would result in a lowering of the regulated systemic pressure (55). Since heart rate is slightly elevated after an initial bradycardia and cardiac strength is reportedly unimpaired in response to endotoxin, the decreased cardiac output is reportedly due to an impeded venous return (4). The alleged fluid efflux would contribute to the decreased venous return. Certain blood borne substances such as serotonin, catecholamines, and histamine have been implicated as causing venoconstriction. Increased postcapillary resistance combined with decreases in responsiveness to pressor agents of peripheral precapillary vessels and the action of vasodilator metabolites, has been reported to facilitate fluid efflux and to participate in decreasing venous return and in a transient waning of total peripheral resistance (3, 4, 34, 54, 57). These effects, especially those of the increased metabolites are said to be the result of stagnant anoxia (3, 4) which may occur in response to intravascular coagulation and low nutritional blood flow (18).

In conclusion, this study is an attempt to provide definitive information on the vascular response in skin and

skeletal muscle to tranfusion during endotoxin shock. Transfusion is an often used procedure in the management of endotoxemia, and although sometimes beneficial in maintaining blood pressure, has not been found to alter the ultimate irreversible course of endotoxin shock. It has been reported that transfusion may lead to fluid loss from blood to tissue by filtration from microvascular sites (51). Skeletal muscle could provide a large reservoir for fluid efflux since it comprises approximately 65% of total body weight. Although a previous study by Weidner et al. provides no evidence for the hypothesis that fluid efflux to skin or skeletal muscle is a factor in determining irreversibility in endotoxin shock (61), transfusion may sufficiently alter hemodynamic relationships in these tissues so as to allow fluid efflux to occur. In light of certain inconsistencies in the literature surrounding the site of alleged fluid losses during endotoxin shock, it is felt that an examination of the responses of skin and skeletal muscle vasculature to transfusion during endotoxin shock is warranted. We have attempted to measure transcapillary fluid fluxes in skin and skeletal muscle utilizing a gravimetric technique. Continuous recordings of forelimb weight and calculations of forelimb skin, skeletal muscle, and total vascular resistances in both precapillary and postcapillary vascular segments were made in an effort to determine the direction and mechanism of transvascular fluid fluxes.

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CHAPTER III

STATEMENT OF THE HYPOTHESIS

The objective of the following study is to test the hypothesis that transvascular fluid efflux into skin and skeletal muscle occurs following transfusion during prolonged endotoxin induced hypotension and to provide meaningful and utilitarian scientific data with regard to the mechanism causing any observed fluid movement.

CHAPTER IV

METHODS

Fourteen dogs of either sex having an average weight of 18 Kg were anesthetized with sodium pentobarbital (30-35 mg/Kg) and allowed to breathe spontaneously through a cuffed endotracheal tube. Skin of the right forelimb was circumferentially sectioned 3-5 cm above the elbow. The right brachial artery, forelimb nerves, and brachial and cephalic veins were isolated, and the muscles and remaining connective tissue sectioned by electrocautery. The humerous was cut and the ends of the marrow cavities packed with bone wax. Blood entered the limb only through the brachial artery and exited only through the brachial and cephalic veins. The forelimb nerves (median, ulnar, radial and musculocutaneous) were left intact and coated with an inert silicone spray to prevent dessication. Heparin was administered in an initial dose of 10 mg/Kg and hourly supplements of 2.5 mg/Kg. The following cannulations were made to obtain segmental pressure gradients in skin and skeletal muscle: (1) skin small artery from the third superficial volar metacarpal artery on the underside of the paw; (2) muscle small artery from a vessel supplying a flexor muscle in the upper portion of the

forelimb; (3) skin small vein from the second superficial dorsal metacarpal vein on the upper surface of the paw; (4) muscle small vein from one of the deep vessels draining a flexor muscle in the middle portion of the forelimb; (5) skin large vein from the cephalic vein via a side branch at the level of the elbow; and (6) muscle large vein from the brachial vein via a side branch at the level of the elbow. All cannulas were small bore polyethylene tubes (PE-10 to PE-60) and cannulation was accompanied using the wedge pressure technique. With this technique the cannulated small vessel acts as an extension of the catheter, and hence, the pressure measured is that in the first collateral vessels joined by the cannulated vessel. The measured pressure is a lateral pressure as long as the cannulated vessel is patent and is not a terminal vessel (this is verified by the ability to freely withdraw blood from and to flush into the vessel). The presence of the catheter does not measurably alter the pressure because, in the forelimb, the cannulated vessel is a negligible fraction of the total cross-sectional area of the vascular bed and there are many artery to artery and vein to vein anastomoses (15, 16, 41). Pressures were measured with low volume displacement Statham transducers (P23G-B) and recorded on a Hewlett-Packard direct-writing oscillograph.

Brachial and cephalic veins were partially transsected 3-5 cm downstream from the site of the large vein pressure measurement and the distal end of each vessel was catheterized with a short section of PE-320 tubing. Total venous outflow was directed into a reservoir maintained at constant volume by a pump which returned shed blood to the left femoral vein. Blood flow was determined by timed collections of the two venous outflows. In this preparation the median cubital vein represents the major anastomotic channel between brachial and cephalic veins. This vessel was ligated and used for large vein pressure measurements, one catheter directed to the cephalic vein, the other to the brachial vein. Thus, brachial venous outflow was predominantly from skeletal muscle while cephalic vein flow was predominantly from skin. Although this approach may not completely isolate the blood flow through the skin from that through muscle, flow separation is sufficient to compare resistance changes in the two parallel-coupled vascular beds (6, 14, 46).

After cannulation the limb was placed on a wire mesh platform attached to a strain-gauge balance (52). In all experiments the balance was calibrated by the addition of a two-gram weight, which produced a 10 to 20 mm pen deflection on the oscillograph. Calibrations were made before each flow measurement. Right atrial pressure was continuously monitored from a catheter (PE-320) in the right

jugular vein. Mean systemic arterial pressure was continuously monitored from a catheter (PE-240) in the right femoral artery which had been advanced to the region of the abdominal aorta. Following a short control period either 20 cc of normal saline or purified E. coli endotoxin (5 mg/Kg) (Difco Laboratories, Detroit, Mich.) suspended in 20 cc of normal saline, was infused into a cannulated saphenous vein by means of a Harvard constant infusion pump. Seven dogs received endotoxin and served as experimental animals, while the seven dogs given saline were control animals. Infusion time was 10 minutes. Limb weight was continuously monitored and all pressures and blood flows were determined twice during a preinfusion control period and thereafter for every 15th minute up to minute 120. At minute 120, 1000 cc of whole blood was administered in a 25 minute transfusion by the means of a Sigmamotor pump. The blood was heparinized and cross-matched. Blood pressures and flows were determined at the second, fifth, tenth and fifteenth minutes after the onset of transfusion and every fifteen minutes thereafter for the duration of the four hour experimental period.

Total and segmental vascular resistances (large arterial, small vessel, large venous) in skin and muscle were calculated by dividing cephalic or brachial blood flow into the corresponding pressure gradient. In addition,

resistances in the total forelimb and in each of the combined skin and muscle segments were calculated as (14, 46):

$$\text{Total forelimb resistance} = \frac{R_{ts} \cdot R_{tm}}{R_{ts} + R_{tm}} \quad (1)$$

$$\text{Total forelimb large artery resistance} = \frac{R_{sa} \cdot R_{ma}}{R_{sa} + R_{ma}} \quad (2)$$

$$\text{Total forelimb small vessel resistance} = \frac{R(s\text{-}v)_s \cdot R(s\text{-}v)_m}{R(s\text{-}v)_s + R(s\text{-}v)_m} \quad (3)$$

$$\text{Total forelimb large vein resistance} = \frac{R_{sv} \cdot R_{mv}}{R_{sv} + R_{mv}} \quad (4)$$

where:

R = resistance in mm Hg x min^{-1} x ml^{-1} x 100 g^{-1}

t = total

s = skin

m = skeletal muscle

a = large artery

s-v = small vessel

v = large vein

Mean transmural pressure in each segment was obtained by: $P_1 + P_2/2$, where: P_1 = inflow pressure; P_2 = outflow pressure.

Hematocrit ratios were determined at minutes 0, 60, 120, 135, and 240 in triplicate by the microcapillary technique.

Since right atrial pressure and vascular resistance in the downstream veins between the elbow and right atrium can affect capillary hydrostatic pressure, the brachial and cephalic veins were left intact in some experiments. These fourteen animals were otherwise prepared in the same manner as described above, however, in these experiments only forelimb weight and segmental vascular pressures were measured. Seven of these animals were administered endotoxin, while seven others served as saline controls.

The mean and the standard error of the mean was calculated for all data obtained. The paired "t" test was used to compare data in each group. The unpaired "t" test was used to compare data between control animals and the experimental groups. A statistically significant difference at the $P < 0.05$ level by the paired or unpaired "t" test was considered true differences between and within the groups.

CHAPTER V

RESULTS

Forelimb weight (Tables 1, 3; Figure 1) (intact or cut vein preparations) fell rapidly and significantly in response to endotoxin. Forelimbs continued to lose weight until minute 120, at which time transfusion was begun. Weight increased in response to transfusion until min. 180, after which it again fell continuously for the duration of the experimental period.

Pressures (Tables 1, 3; Figures 2, 3, 6, 7, 8). All vascular pressures (intact or cut vein preparations) fell significantly in response to endotoxin. After transfusion they rose for a variable period of time before again falling until the end of the experimental period (min. 240). Small and large vein pressures in both skin and skeletal muscle rose to values not significantly different from control in response to transfusion. Systemic arterial pressure and small artery pressure in both skin and skeletal muscle remained significantly lower than control throughout the experimental period, as did right atrial pressure. The latter, however, increased to levels not significantly different from pre-endotoxin values after transfusion.

Blood flows (Tables 1, 3; Figures 4, 5). Total forelimb blood flows fell significantly in response to endotoxin, and, after transfusion rose transiently before falling to low values by the end of the experimental period. Both total blood flow and skin blood flow remained significantly lower than control throughout the experimental period. Muscle blood flow, however, rose to values which were not significantly different than control before returning to values significantly different from controls.

Resistances (Tables 1, 3; Figures 9-16). All vascular resistances (total forelimb vascular resistances, total segmental vascular resistances and skin and skeletal muscle segmental vascular resistances) increased significantly in response to endotoxin, and, after transfusion decreased for variable periods of time before increasing again until minute 240. Total forelimb vascular resistance, total forelimb large artery resistance and total forelimb small vessel resistance fell to values which were not significantly different than control in response to transfusion. These parameters reached values which were significantly different from control by the end of the experimental period. Total forelimb large vein resistance remained significantly above control throughout the experimental period. Total skin vascular resistance remained significantly above control throughout the experimental period, while total muscle

vascular resistance transiently decreased to values which were not significantly different than control after transfusion but later increased significantly. Skin large arterial resistance fell to a level not significantly different from control only at min. 135, while muscle large arterial resistance remained at values not significantly different from control for a transient period before rising to significant levels near the end of the experimental period. Skin small vessel resistance and muscle small vessel resistance both fell to values not significantly different from control after transfusion, however, while small vessel resistance in muscle was significantly below control for a transient period, that in skin increased to significant values by the end of the 240 minute period. Similar results were seen in skin and muscle venous resistances; muscle venous resistance reached values for a transient period after transfusion which were not significantly different from control while that in skin remained significantly different throughout the experimental period.

Hematocrits (Table 5). Hematocrits (intact and cut vein preparation) increased progressively throughout the experimental period.

Control animals (Table 2, Figures 1-16). No significant changes were seen in saline control animals from the

beginning of the experimental period until minute 120. Following transfusion significant increases were observed in forelimb weight, small vein pressure in skin and muscle and right atrial pressure. The weight gain in control animals was approximately 22 grams. The increases in all pressures were transient and pressures fell toward the end of the experimental period. No significant increases in resistance were observed.

Intact vein preparations (Tables 3, 4). The responses of both animals administered endotoxin and control animals in this group to transfusion was essentially the same as corresponding animals with the cut vein preparation.

Figure 1. Effect of transfusion on forelimb weight (9) in endotoxin animals (closed circles, N = 7) and saline control animals (closed triangles, N = 7). Endotoxin (5 mg/Kg in 20 cc of saline) and saline (20 cc) were given at minute 0 as a ten-minute infusion. Transfusion of whole blood (1000 cc/25 minutes) was begun at minute 120. Open circles denote statistical significance at $p < 0.05$. Bars denote standard error.

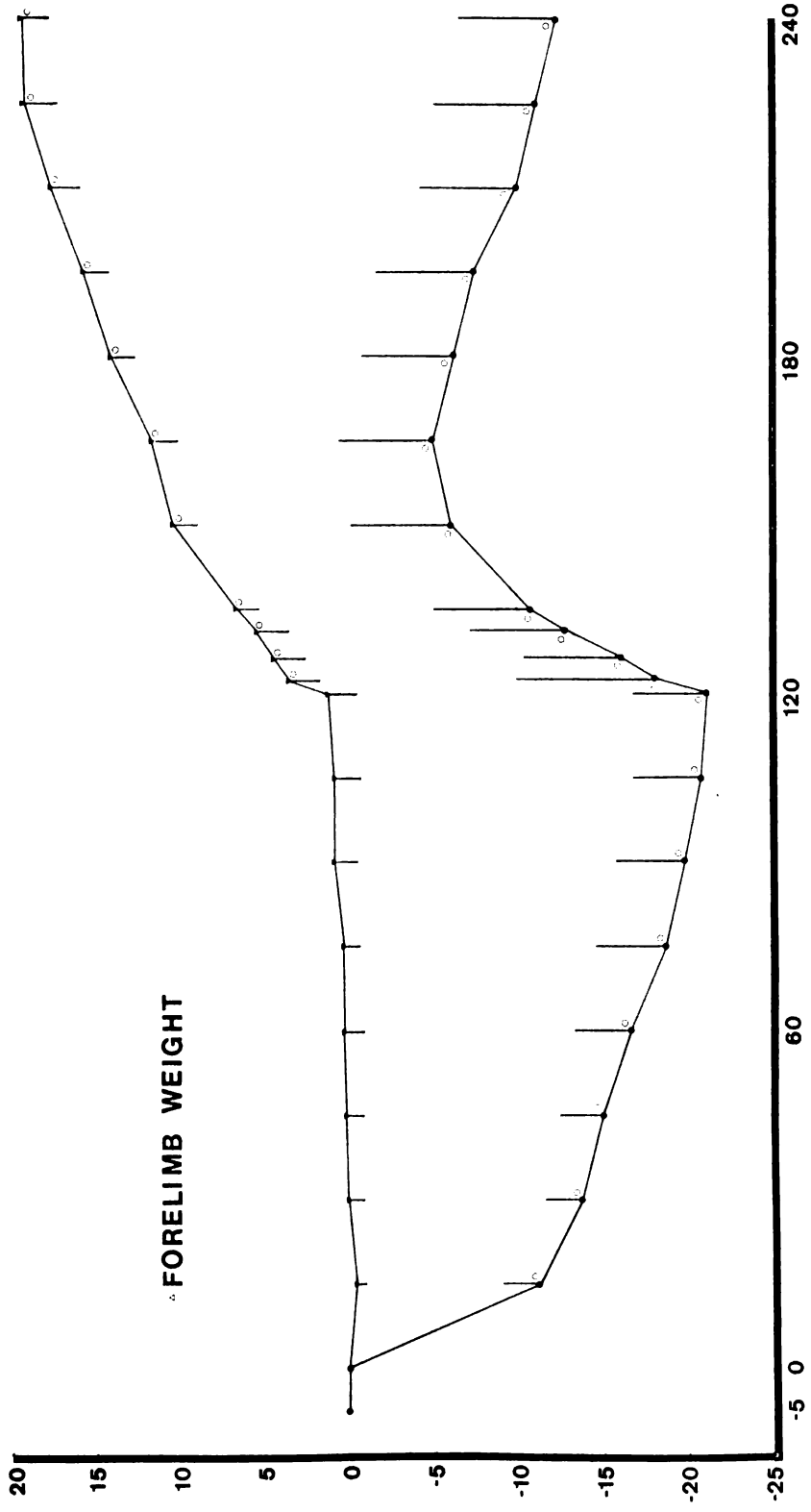

Figure 1

Figure 2. Effect of transfusion on systemic arterial pressure (mm Hg) in endotoxin animals and saline control animals. All symbols, N values, and dosages correspond to Figure 1.

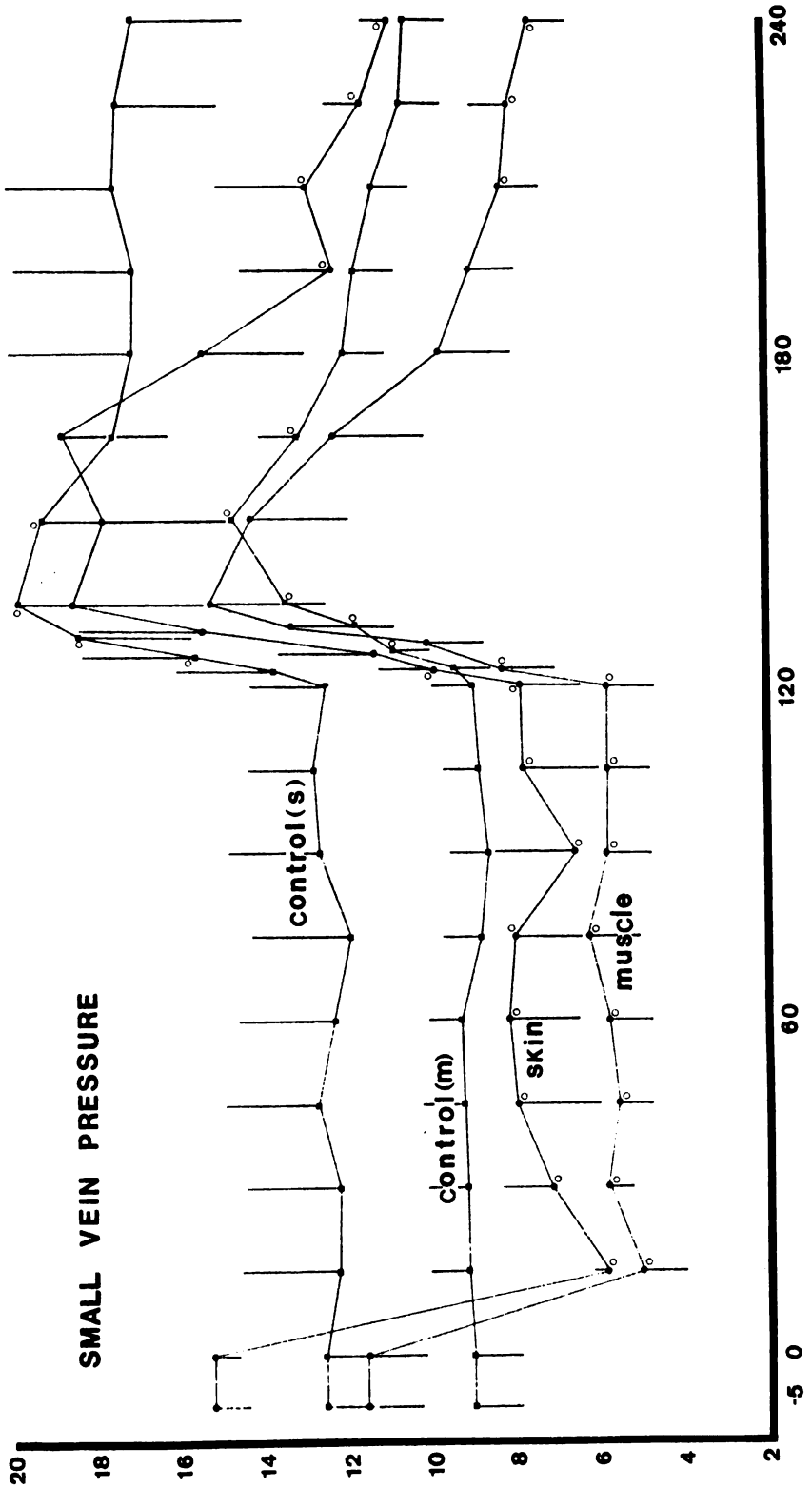
SMALL VEIN PRESSURE
20
18
16
14
12
10
8
6
4
2
-5
0
60
120
180
240
control(s)
control(m)
skin
muscle

Figure 6

Figure 7. Effect of transfusion on forelimb skin and muscle small artery pressure (mm Hg) in endotoxin and saline control animals. All symbols, N values, and dosages correspond to Figure 5.

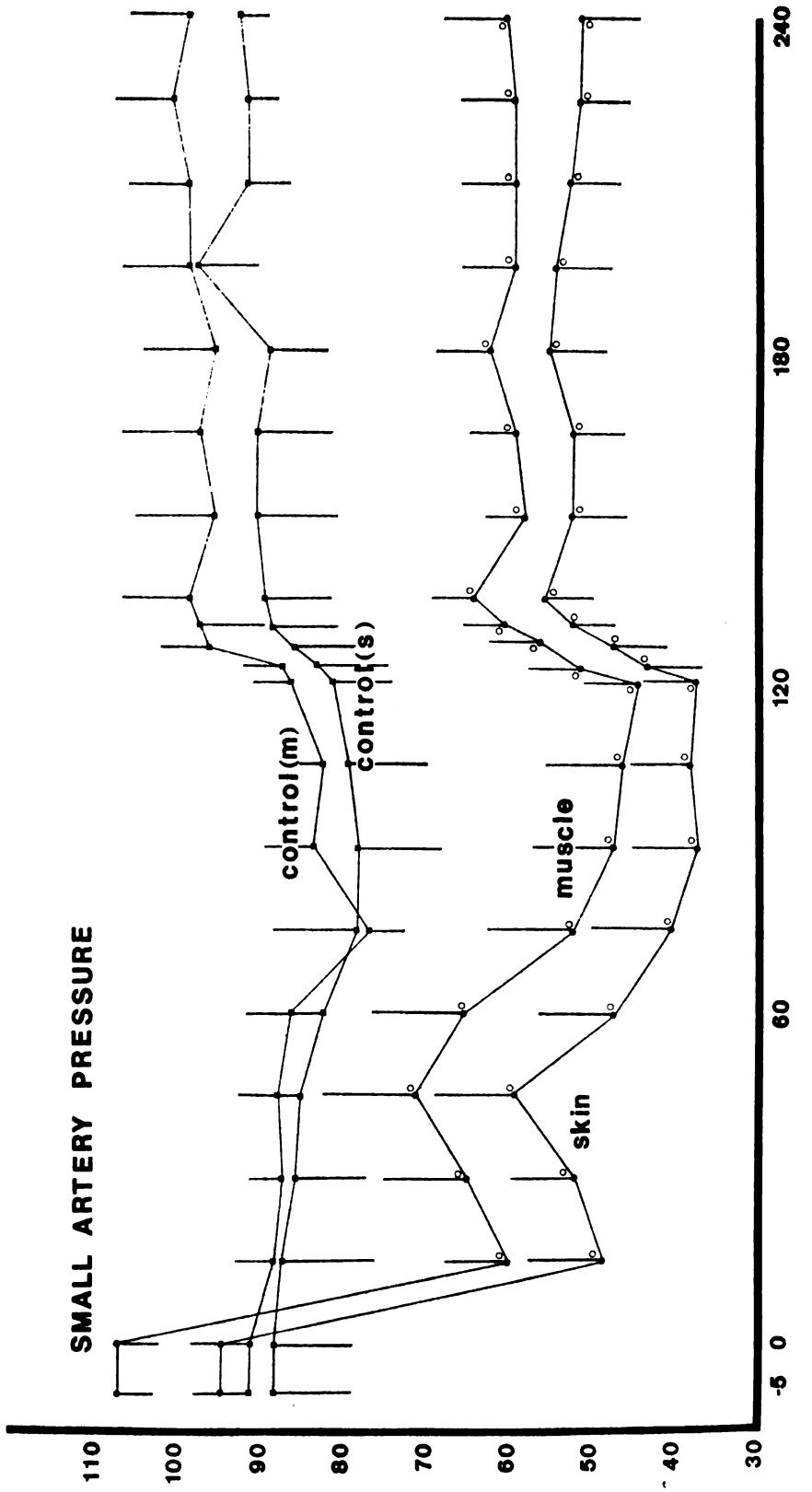
SMALL ARTERY PRESSURE
110
100
90
80
70
60
50
40
30
-5
0
60
120
180
240
control(m)
control(s)
muscle
skin

Figure 7

Figure 8. Effect of transfusion on forelimb skin and muscle large vein pressure (mm Hg) in endotoxin and saline control animals. All symbols, N values, and dosages correspond to those in Figure 5.

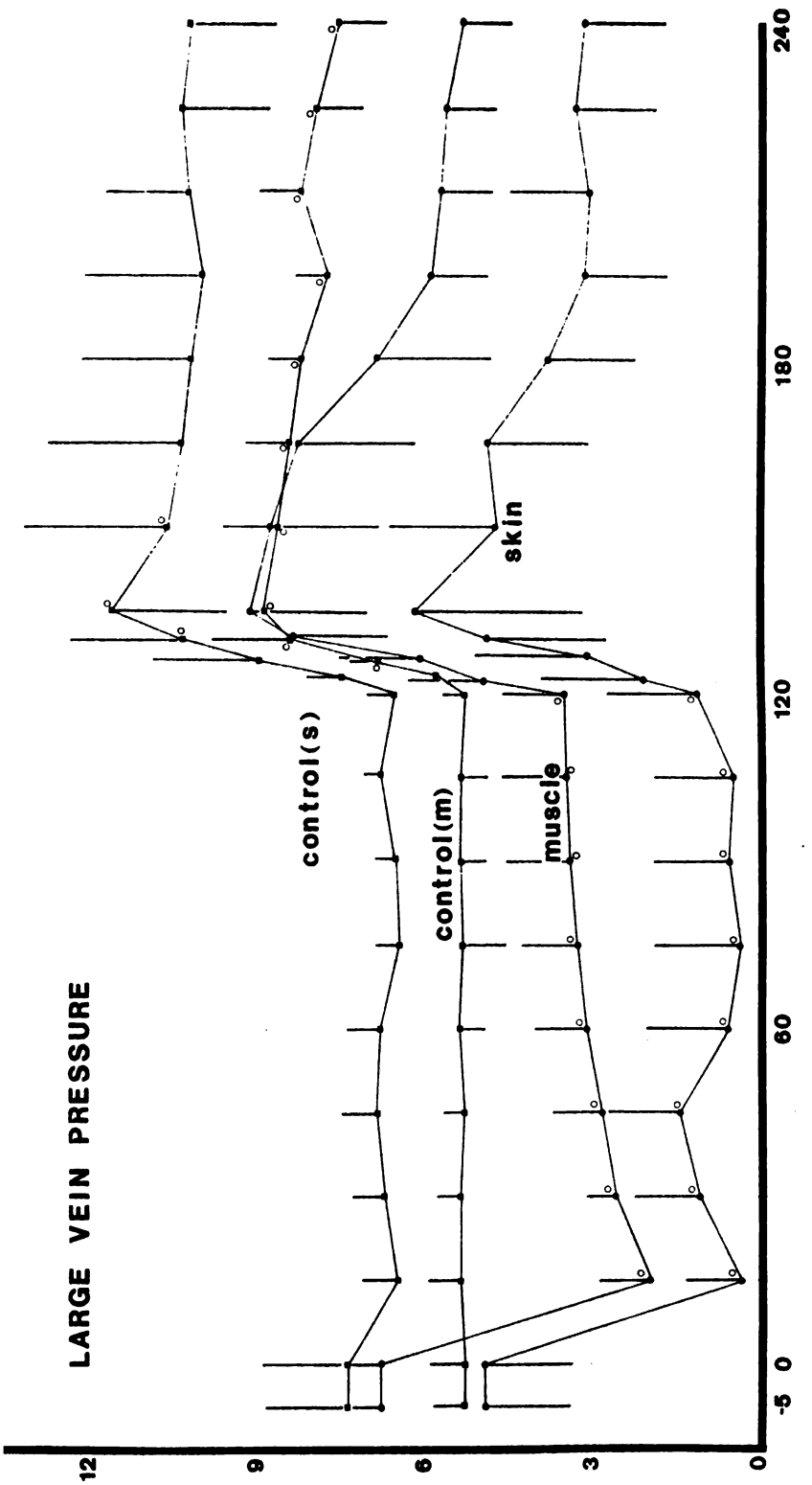
LARGE VEIN PRESSURE
12
9
6
3
0
-5
0
60
120
180
240
control(s)
control(m)
muscle
skin

Figure 8

Figure 9. Effect of transfusion on total forelimb resistance (mm Hg/ml/min/100 g forelimb) in endotoxin animals and saline control animals. All symbols, N values, and dosages correspond to Figure 1.

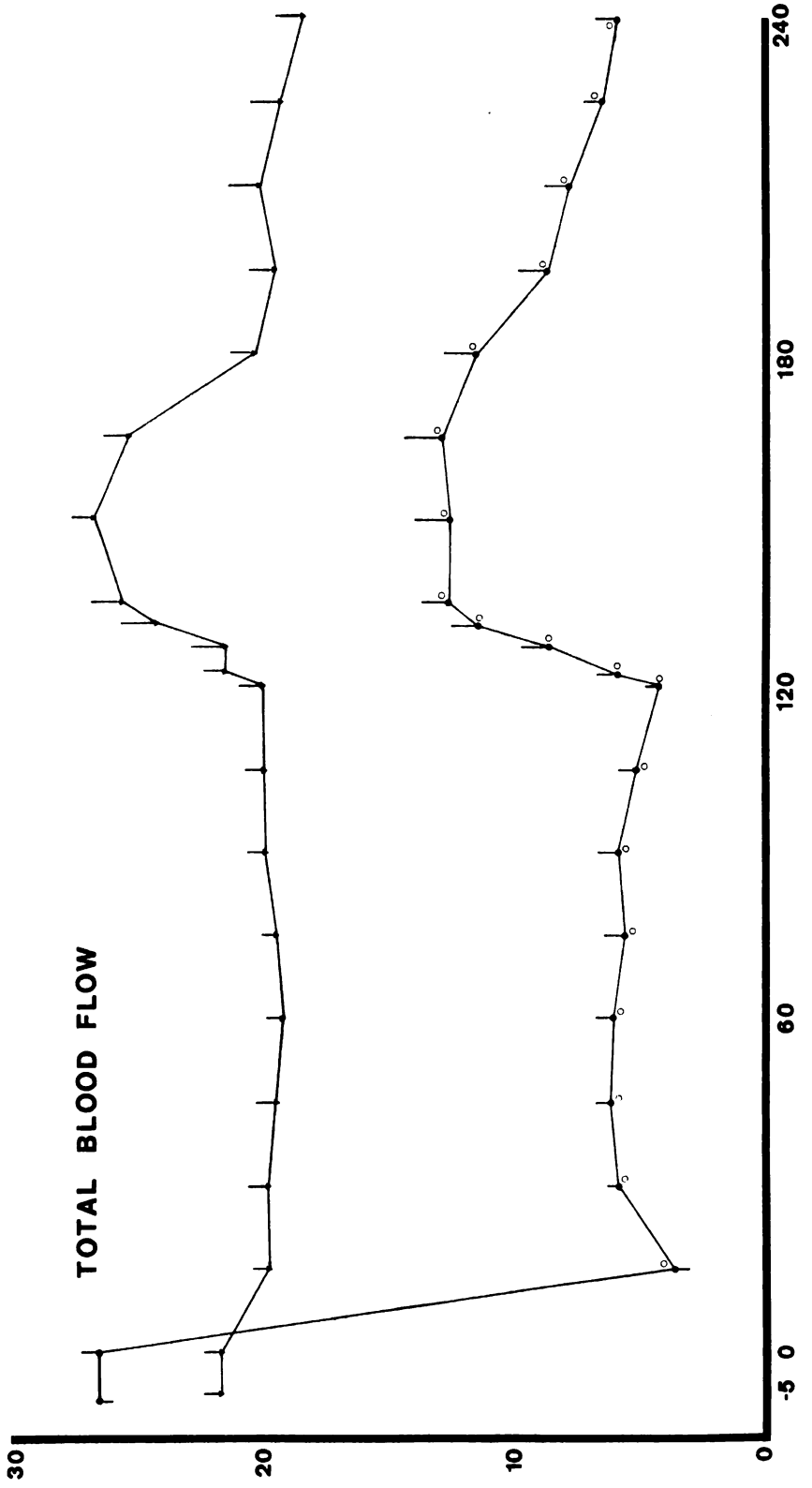

Figure 4

Figure 5. Effects of transfusion on forelimb skin and muscle blood flows (ml/min/100 g forelimb) in endotoxin animals (closed circles) and saline control animals (closed squares). N values, other symbols, and dosages correspond to those in Figure 1.

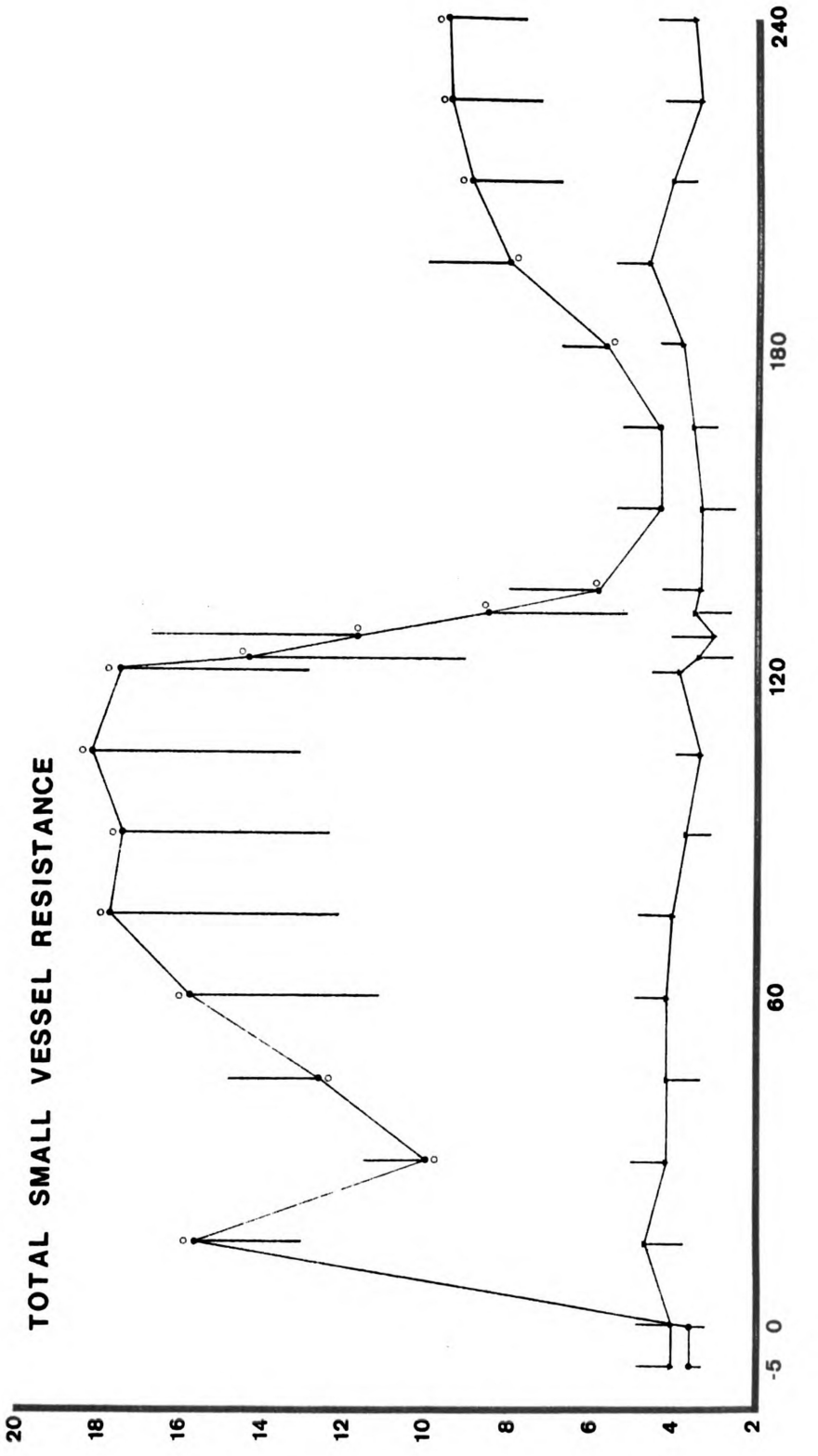
TOTAL SMALL VESSEL RESISTANCE
20
18
16
14
12
10
8
6
4
2
-5
0
60
120
180
240

Figure 10

Figure 6. Effects of transfusion on forelimb skin and muscle small vein pressures (mm Hg) in endotoxin and saline control animals. All symbols, N values and dosages correspond to Figure 5.

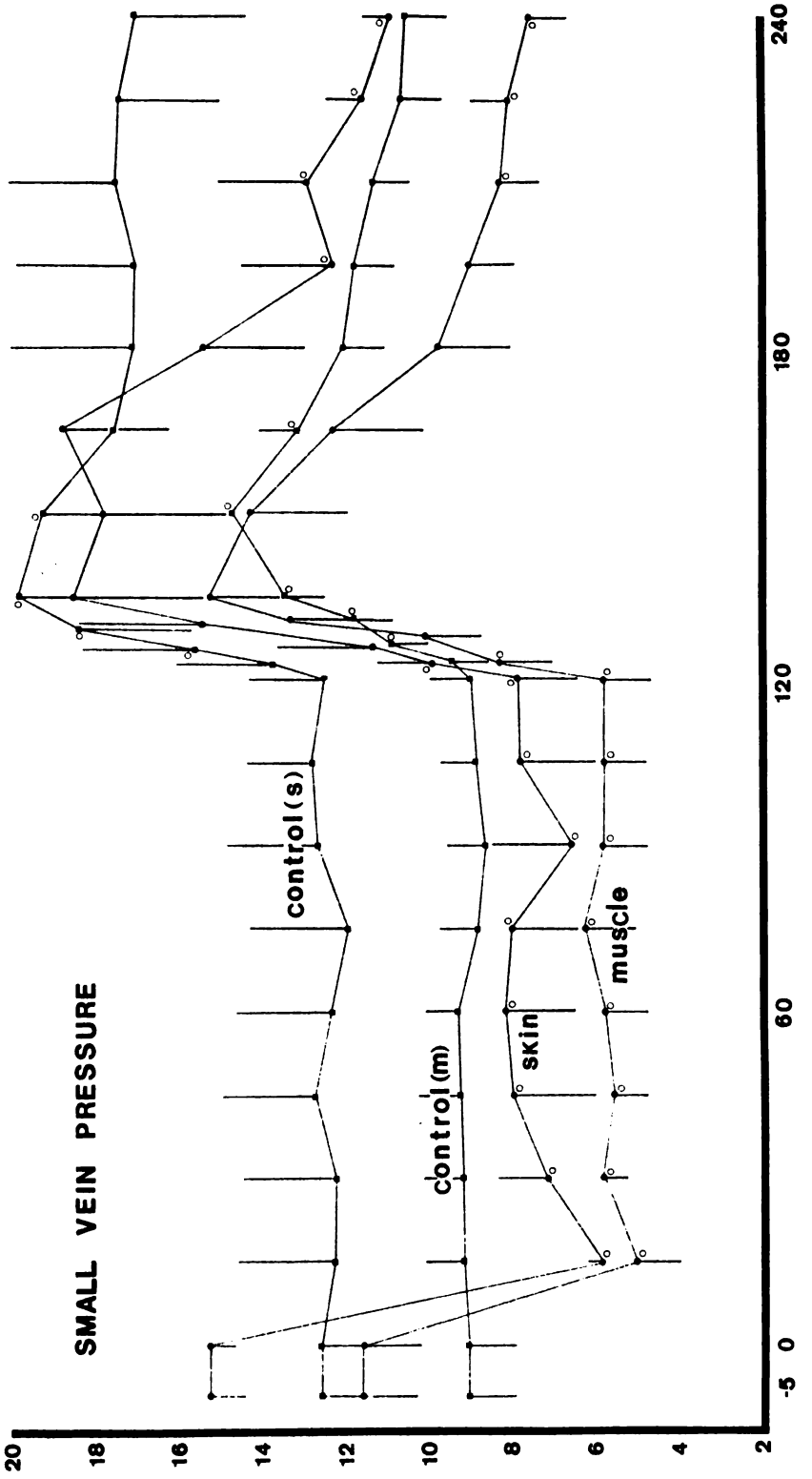
SMALL VEIN PRESSURE
20
18
16
14
12
10
8
6
4
2
-5
0
60
120
180
240
control(s)
control(m)
skin
muscle

Figure 6

Figure 7. Effect of transfusion on forelimb skin and muscle small artery pressure (mm Hg) in endotoxin and saline control animals. All symbols, N values, and dosages correspond to Figure 5.

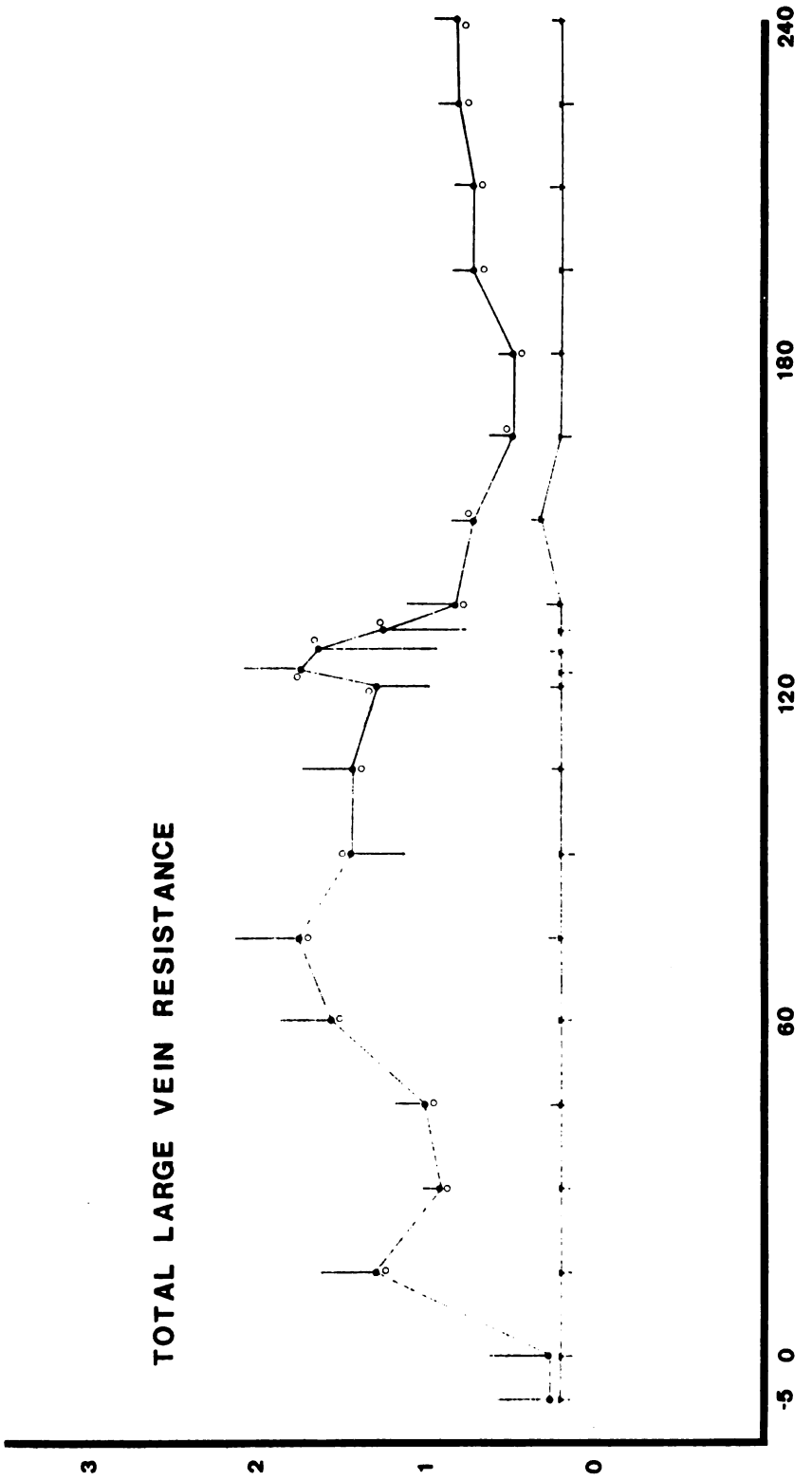

Figure 12

Figure 8. Effect of transfusion on forelimb skin and muscle large vein pressure (mm Hg) in endotoxin and saline control animals. All symbols, N values, and dosages correspond to those in Figure 5.

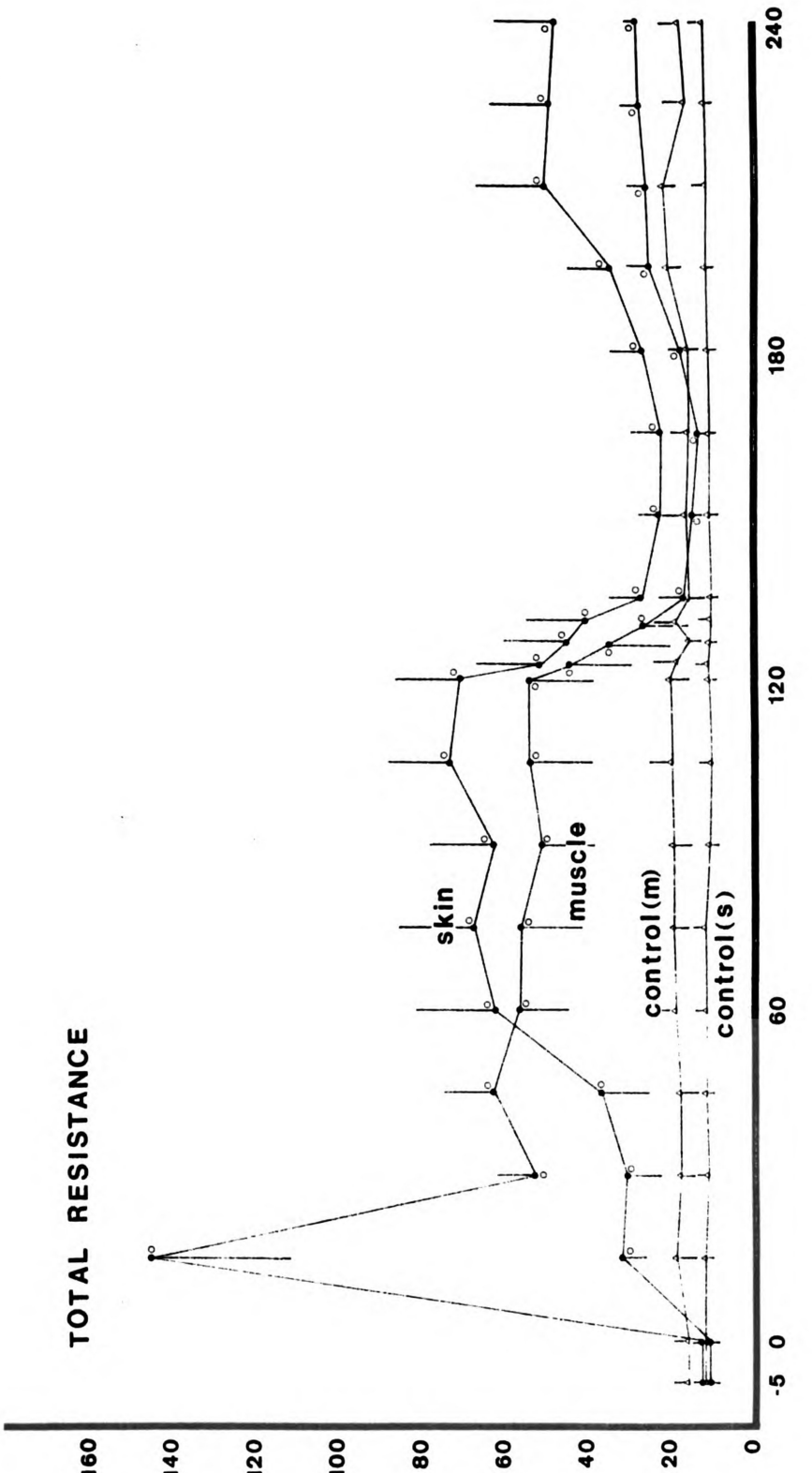
TOTAL RESISTANCE
160
140
120
100
80
60
40
20
0
-5
0
60
120
180
240
skin
muscle
control(m)
control(s)

Figure 13

Figure 9. Effect of transfusion on total forelimb resistance (mm Hg/ml/min/100 g forelimb) in endotoxin animals and saline control animals. All symbols, N values, and dosages correspond to Figure 1.

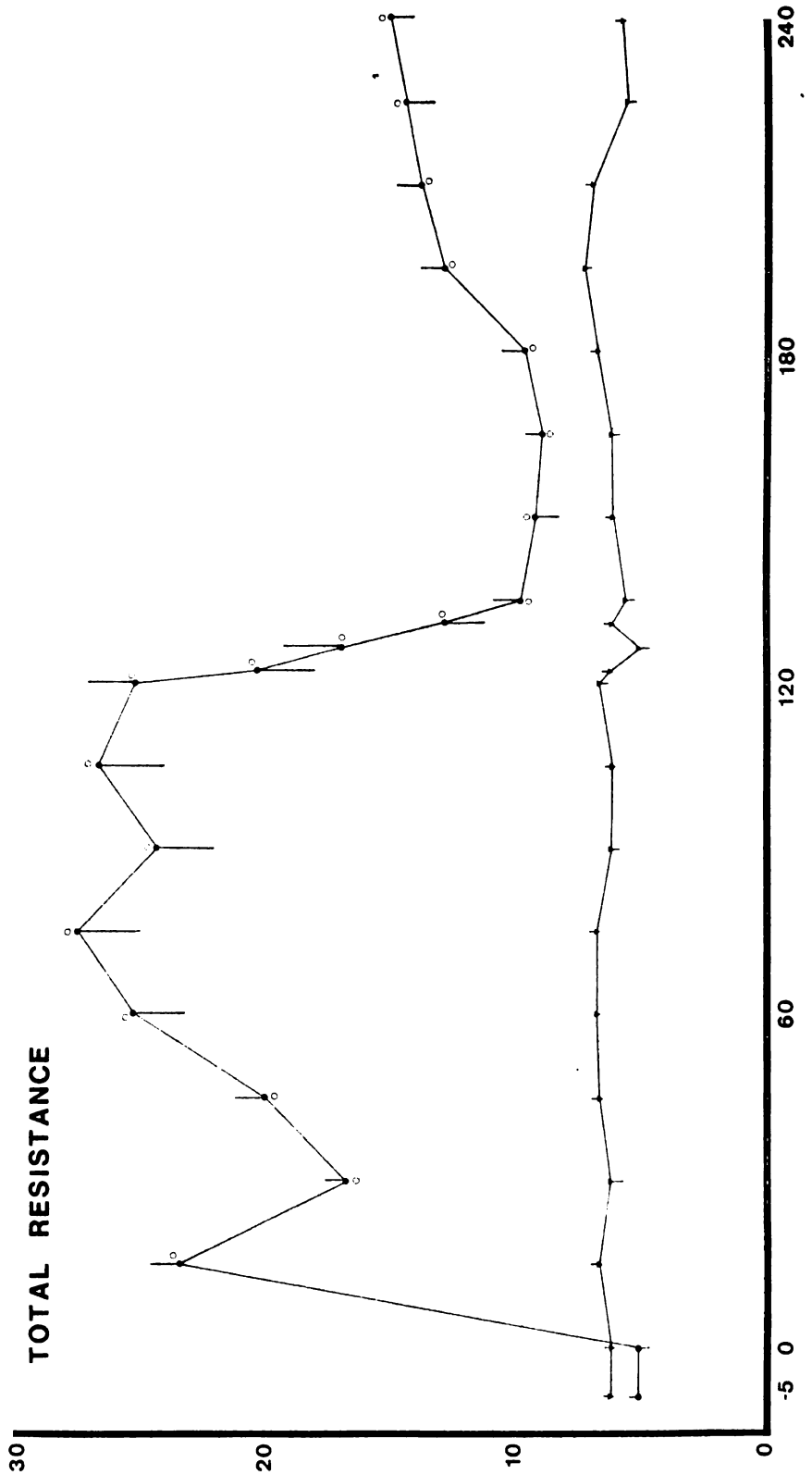

Figure 9

Figure 15. Effect of transfusion on forelimb skin and muscle large artery resistance (mm Hg/ml/ min/100 g forelimb) in endotoxin and saline control animals. All symbols, N values, and dosages correspond to Figure 13.

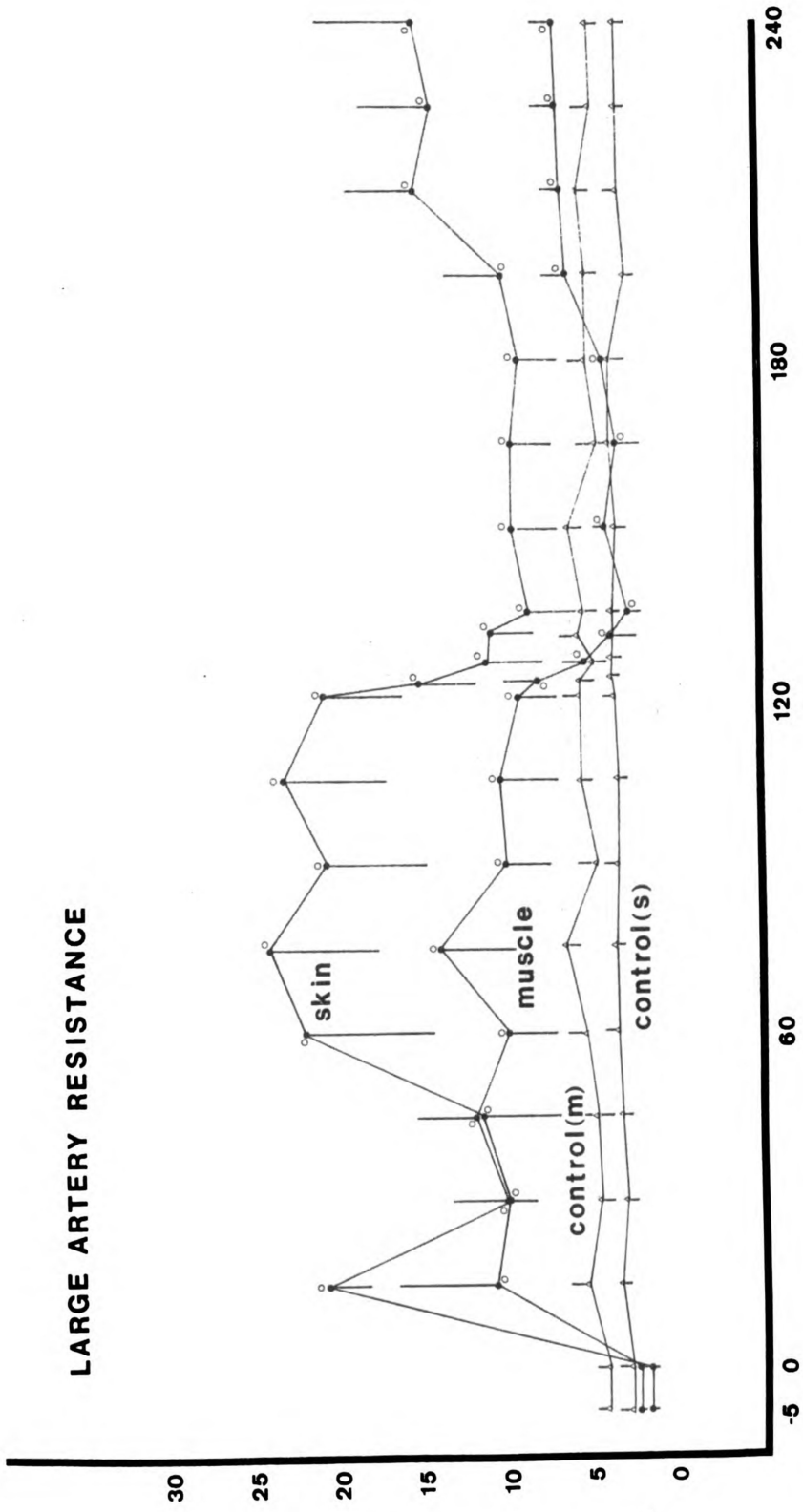
LARGE ARTERY RESISTANCE
30
25
20
15
10
5
0
-5
0
60
120
180
240
skin
muscle
control(m)
control(s)

Figure 15

Figure 11. Effect of transfusion on total forelimb large artery resistance (mm Hg/ml/min/100 g forelimb) in endotoxin and saline control animals. All symbols, N values and dosages correspond to those in Figure 1.

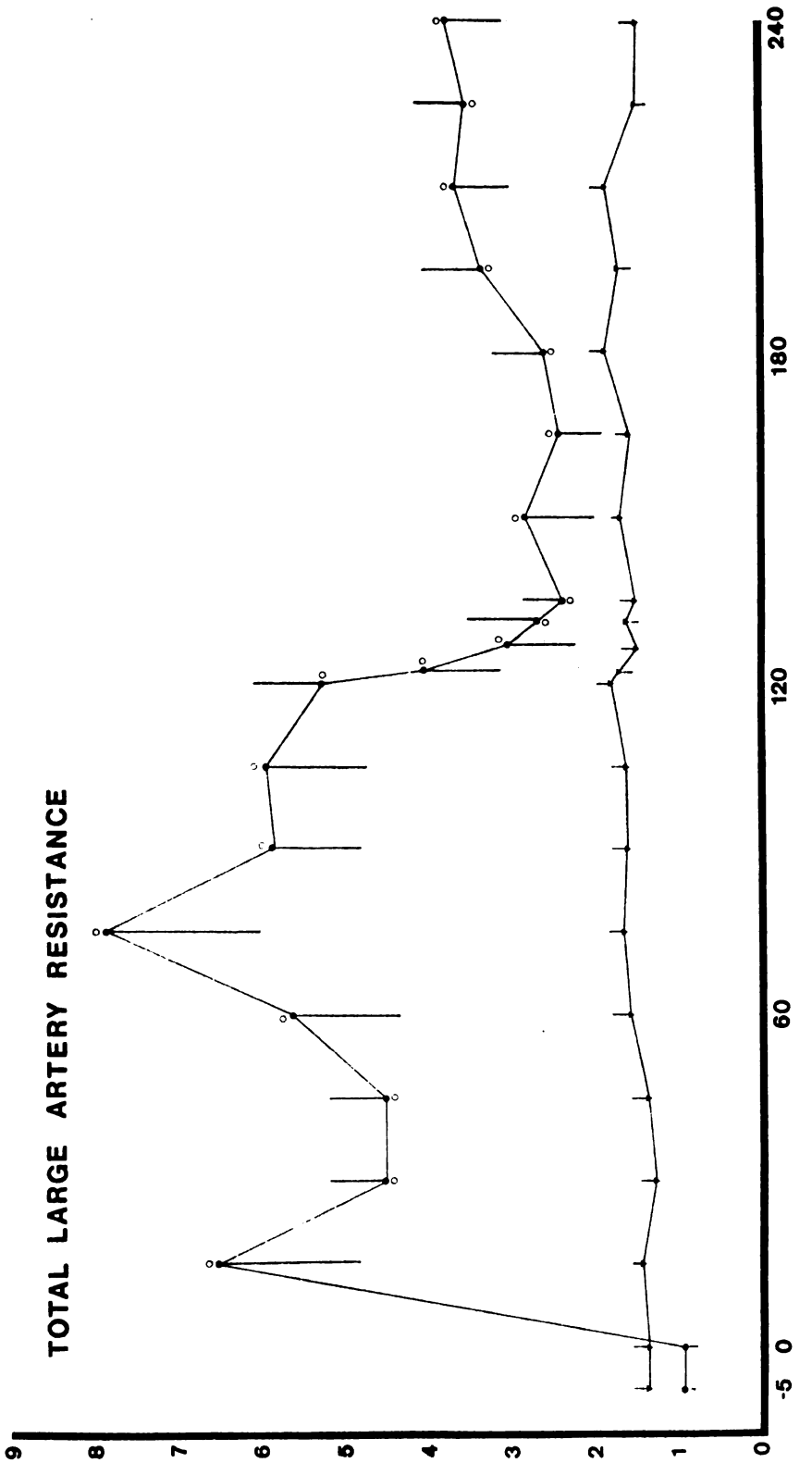

Figure 11

Figure 16. Effect of transfusion on forelimb skin and muscle large vein resistance (mm Hg/ml/min/ 100 g forelimb) in endotoxin animals and saline control animals. All symbols, N values, and dosages correspond to those in Figure 13.

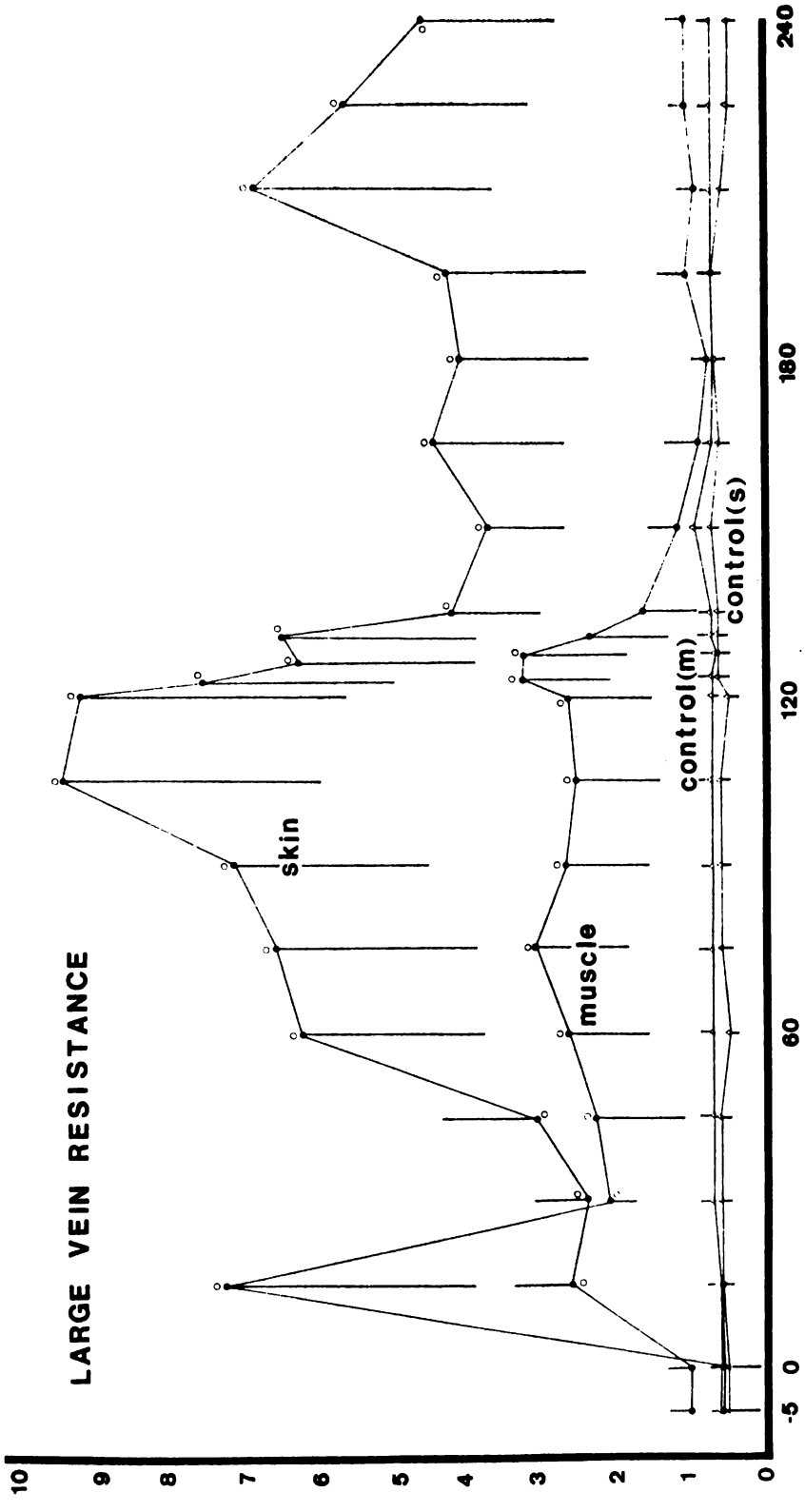
LARGE VEIN RESISTANCE
skin
muscle
control(m)
control(s)
10
9
8
7
6
5
4
3
2
1
0
-5
0
60
120
180
240

Figure 16

Key to Tables 1, 2, 3, 4

Complete data from control and experimental groups. All data presented as mean value ± standard error. The following abbreviations were used:

Accum wt = change in forelimb weight

A.P. = systemic arterial pressure

Pssv = small skin vein pressure

Plsv = large skin vein pressure

Pssa = skin artery pressure

Psmv = small muscle vein pressure

Plmv = large muscle vein pressure

Psma = muscle artery pressure

Fs/100g = skin blood flow per 100 g forelimb

Fm/100g - muscle blood flow per 100 g forelimb

Rsa = skin arterial resistance

R(s-v)s = skin small vessel resistance

Rsv = skin venous resistance

Rms = muscle arterial resistance

R(s-v)m = muscle small vessel resistance

Rmv - muscle venous resistance

Rmt = total muscle resistance

Rst = total skin resistance

Rat = total arterial resistance

R(s-v)t = total small vessel resistance

Rvt = total venous resistance

Rt = total resistance

Tp(A)s = skin arterial transmural pressure

Tp(s-v)s = skin small vessel transmural pressure

Tp(V)s = skin venous transmural pressure

Tp(A)m = muscle arterial transmural pressure

Tp(s-v)m = muscle small vessel transmural pressure

Tp(V)m = muscle venous transmural pressure

Accum wt is given in grams; all pressures in mm Hg; blood flows in ml/min/100 g forelimb; resistance in mm Hg/ml/min/100 g forelimb.

Table 1. Effect of transfusion (1000 cc whole blood/25 minutes) in animals previously administered endotoxin (5 mg/Kg/20 cc saline) in a 10-minute infusion. Endotoxin was administered at minute 0, transfusion began at minute 120. Asterisk denotes statistical significance (difference from time "0" in pre-endotoxin period) at the $p < 0.05$ level. $N = 7$; limb wt 474.7 ± 16.01 g; brachial and cephalic veins cut.

Table 1

time	Accum. wt.	A.P.	Pssv	Plsv	Pssa	Fs/100g	Psmv
-5	0.0±0.00	125.2± 4.78	15.4±1.33	4.7±1.75	94.7±3.17	14.2±2.24	11.7±1.32
0	0.2±0.19	125.4± 4.71	15.4±0.90	4.7±1.75	94.8±3.22	14.3±2.24	11.7±1.32
15	-12.0±1.80*	71.0± 7.51	5.8±0.31*	0.4±0.89*	48.0±8.06*	2.5±0.57*	4.8±0.94*
30	-14.0±1.94*	79.5± 8.45	6.7±1.14*	1.0±0.99*	52.2±7.37*	3.1±0.56*	5.7±0.53*
45	-15.5±2.23*	87.0±10.96*	7.9±1.83*	1.2±1.35*	59.0±9.35*	3.3±0.89*	5.6±0.69*
60	-17.1±3.37*	78.8±11.18*	8.1±1.70*	0.6±1.44*	47.8±8.66*	3.0±1.36*	5.8±0.84*
75	-19.0±4.13*	67.8±10.91*	7.0±1.44*	0.4±1.50*	40.7±9.16*	2.5±1.34*	6.1±0.95*
90	-20.1±4.29*	59.7±10.14*	6.5±1.38*	0.5±1.33*	37.8±7.88*	2.1±1.31*	5.7±0.87*
105	-21.0±4.43*	58.4± 8.26*	6.8±1.37*	0.5±1.40*	38.4±7.12*	1.7±1.04*	5.8±0.86*
120	-21.7±4.49*	54.8± 7.68*	6.9±1.44*	1.2±1.60*	37.8±6.86*	1.4±0.76*	5.8±0.98*
122	-18.5±5.39*	63.5± 7.15*	9.5±1.32*	1.9±1.95	43.4±6.55*	2.5±1.35*	8.2±1.15*
125	-16.8±5.40*	68.4± 6.75*	11.2±2.35	3.0±2.21	46.1±5.64*	4.1±2.15*	10.4±1.56
130	-14.1±5.34*	76.4± 5.42*	15.2±2.88	4.6±2.77	52.4±4.74*	4.8±2.27*	13.2±1.75
135	-11.0±5.64*	82.4± 5.79*	18.2±2.70	6.2±2.95	55.5±5.23*	4.2±0.95*	14.8±1.80
150	- 6.7±5.67	80.2± 5.28*	17.8±2.95	4.8±1.79	52.1±5.78*	3.8±0.62*	14.2±2.18
165	- 5.2±5.22	78.4± 7.17*	18.5±2.17	4.8±1.72	52.4±5.62*	4.1±0.86*	12.1±2.10
180	- 6.2±5.42	78.5± 7.02*	15.1±1.27	4.0±1.54	54.1±5.81*	4.2±1.02*	9.7±1.60
195	- 8.4±5.84*	76.5± 6.80*	12.7±1.03*	3.2±1.44	53.2±6.39*	3.4±1.09*	8.7±0.94
210	-10.2±5.64*	76.5± 7.19*	12.6±1.04*	3.0±1.38	52.0±6.36*	2.8±1.10*	8.1±0.83*
225	-11.2±5.78*	75.2± 7.06*	11.7±0.64*	3.3±1.45	51.7±6.30*	2.6±0.90*	8.0±0.85*
240	-12.2±5.76*	76.8± 7.73*	10.9±0.52*	3.0±1.40	51.4±6.71*	2.8±1.09*	7.8±0.99*

*p < 0.05

Table 1--Continued

time	Plmv	Psma	Fm/100g	Ft/100g	Rap	Rsa	R(s-v)s
-5	6.9±1.04	107.1± 3.92	11.4±1.27	25.7±1.60	2.1±0.38	2.2±0.24	6.7± 1.35
0	6.9±1.04	107.1± 3.92	11.4±1.27	25.7±1.60	2.1±0.38	2.2±0.26	6.6± 1.35
15	1.7±0.62*	60.7± 7.13	1.1±0.53*	3.6±1.00*	0.4±0.58*	11.2±2.02*	18.5± 3.09*
30	2.6±0.49*	64.5± 9.77*	1.7±0.35*	4.8±0.72*	0.2±0.61*	10.1±3.60*	16.6± 4.16*
45	2.9±0.70*	71.4±11.09*	1.9±0.63*	5.3±1.32*	0.2±0.61*	11.9±7.14*	21.1± 5.95*
60	3.1±0.87*	64.5±10.42*	2.1±0.70*	5.1±1.86*	-0.2±0.66*	22.6±7.13*	32.0±10.42*
75	3.3±0.88*	52.3±10.37*	1.8±0.57*	4.4±1.78*	-0.6±0.61*	24.9±5.82*	33.8±11.63*
90	3.4±0.90*	47.7± 9.12*	1.8±0.58*	3.9±1.59*	-0.6±0.75*	21.7±5.61*	32.6± 9.62*
105	3.6±0.90*	46.9± 8.14*	1.9±0.70*	3.6±1.37*	-0.4±0.78*	23.8±5.81*	39.3±12.31*
120	3.6±0.90*	44.7± 6.89*	2.0±0.83*	3.4±1.23*	-0.4±0.74*	21.0±4.23*	37.6±10.61*
122	4.8±1.08	51.4± 6.60*	2.9±1.26*	5.5±1.96*	-0.1±0.81*	15.2±3.69*	29.0± 9.81*
125	6.1±1.25	55.0± 6.09*	4.1±1.61*	8.2±2.73*	0.4±0.67*	11.7±3.73*	25.2±10.53*
130	8.1±1.65	60.2± 4.65*	6.3±2.48	11.2±3.36*	1.3±0.55	11.0±1.74	23.3± 8.03*
135	9.7±2.04	63.0± 5.16*	7.8±3.21	12.1±3.37*	1.6±0.66	8.0±3.41*	13.5± 4.07
150	8.7±1.72	58.5± 4.78*	8.5±4.07	12.4±4.36*	1.9±0.82	9.9±2.41*	9.5± 1 33
165	8.3±1.80	59.4± 5.76*	8.6±4.05	12.7±4.40*	2.4±1.24	9.1±2.17*	10.3± 2.28
180	6.7±1.46	62.1± 6.41*	6.7±3.30	11.0±3.65*	1.2±1.02	8.5±2.15*	13.1± 3.82*
195	5.9±0.81	59.7± 6.60*	5.2±2.68*	8.6±2.99*	1.4±0.99	10.1±2.98*	19.0± 5.93*
210	5.7±0.73	59.0± 6.75*	4.4±1.89*	7.2±2.01*	1.2±1.01	15.4±4.38*	27.5± 9.78*
225	5.6±0.77	59.7± 6.87*	3.4±1.21*	6.0±1.29*	1.0±0.95	14.4±4.11*	26.3± 8.19*
240	5.2±0.77	60.4± 7.22*	3.0±0.60*	5.8±1.19*	1.1±0.93	15.3±5.12*	24.7± 7.40*

*$p < 0.05$

Table 1--Continued

time	Rsv	Rst	Rma	R(s-v)m	Rmv	Rmt	Rat
-5	0.9±0.25	9.9± 1.66	1.7±0.26	9.0± 1.05	0.4±0.52	11.2± 1.33	0.9±0.07
0	0.9±0.25	9.8± 1.67	1.7±0.26	9.0± 1.05	0.4±0.52	11.2± 1.30	0.9±0.07
15	2.5±0.69*	32.3± 4.16*	21.0±6.38*	114.8±26.08*	7.3±2.82*	143.2±33.25*	6.4±1.68*
30	2.2±0.64*	29.1± 6.52*	10.1±1.91*	39.9± 8.71*	2.1±0.26*	52.2± 8.39*	4.4±0.67*
45	3.0±1.09*	36.2±10.39*	12.3±3.20*	48.0±10.77*	2.3±0.91*	62.7±12.31*	4.6±0.67*
60	6.4±2.21*	61.0±18.36*	9.9±2.60	43.7±10.50*	2.5±0.91*	56.2±11.91*	5.6±1.30*
75	6.6±2.31*	65.4±16.98*	14.2±4.37*	39.7± 9.97*	2.9±1.05*	56.9±13.27*	7.8±1.99*
90	7.2±2.17*	61.6±13.82*	10.2±2.25*	38.8± 9.72*	2.5±0.94*	51.5±11.97*	5.8±1.09*
105	9.4±3.02*	72.6±16.63*	10.5±2.99*	41.2±10.32*	2.4±0.93*	54.2±13.05*	5.9±1.36*
120	9.1±3.08*	67.7±14.74*	8.9±1.93*	43.3±11.09*	2.5±0.96*	54.8±13.61*	5.2±0.88*
122	7.5±2.21*	51.9±13.57*	6.9±1.88*	33.7±11.09*	2.9±0.98	43.6±13.22*	4.0±0.94*
125	6.3±2.13*	43.2±14.36*	5.3±1.39*	26.8±11.38	2.9±1.34	35.1±13.93*	2.9±0.77*
130	6.5±2.32*	40.9±13.02*	4.3±1.39*	18.0± 7.06*	2.1±0.89	24.5± 9.02*	2.6±0.84*
135	4.0±1.03*	25.6± 6.09*	3.5±0.67	12.8± 4.67	1.4±0.57	17.9± 5.40	2.3±0.47*
150	3.6±0.80*	23.1± 4.12*	4.1±0.87	10.1± 3.16	1.1±0.33	15.5± 3.60	2.7±0.70*
165	4.4±1.56*	23.9± 5.99*	3.5±0.67	9.1± 1.56	0.8±0.33	13.4± 2.09	2.3±0.48*
180	3.8±1.57*	25.5± 7.17*	3.9±0.87	12.8± 2.11	0.7±0.15	17.5± 2.49	2.4±0.57*
195	4.2±1.60*	33.3± 9.03*	5.8±1.19*	17.9± 3.72*	1.0±0.30	24.8± 4.83*	3.3±0.67*
210	6.9±2.75*	49.9±16.24*	5.9±1.02*	17.5± 3.31*	0.8±0.20	24.3± 3.97*	3.5±0.60*
225	5.6±2.15*	46.4±13.69*	5.9±1.28*	19.6± 3.16*	1.0±0.21	26.6± 3.66*	3.4±0.62*
240	4.8±1.59*	44.9±12.76*	6.0±1.08*	19.1± 2.64*	1.0±0.20	26.2± 2.80*	3.6±0.58*

*p · 0.05

Table 1--Continued

Δ time	R(s-v)t	Rvt	Rt	Tp(A)s	Tp(A)m	Tp(s-v)s	Tp(s-v)m
-5	3.3±0.24	0.2±0.03	4.7±0.28	110.0± 3.56	116.2± 4.30	55.0±2.15	59.4±2.43
0	3.3±0.24	0.2±0.03	4.7±0.28	110.1± 3.56	116.2± 4.27	55.1±2.18	59.4±2.43
15	14.5±2.54*	1.2±0.34*	23.8±3.41*	59.5± 7.57*	65.8± 7.28*	26.9±4.32*	32.7±3.61*
30	10.2±1.47*	0.9±0.11*	16.6±1.77*	65.9± 7.83*	72.0± 9.08*	29.5±3.83*	35.1±4.95*
45	12.5±2.29*	1.0±0.29*	19.2±3.15*	73.0±10.08*	79.2±11.07*	33.5±5.16*	38.5±5.78*
60	15.7±4.68*	1.5±0.56*	25.2±5.99*	63.3± 9.77*	71.7±10.71*	28.0±5.09*	35.2±5.53*
75	16.7±5.38*	1.6±0.61*	27.3±6.67*	54.3± 9.82*	60.1±10.59*	23.8±5.21*	29.2±5.63*
90	16.4±4.74*	1.4±0.56*	24.8±6.02*	48.7± 8.86*	53.7± 9.59*	22.2±4.42*	26.7±4.92*
105	18.1±5.19*	1.4±0.58*	26.6±6.47*	48.4± 7.52*	52.6± 8.13*	22.6±3.99*	26.3±4.40*
120	17.6±4.50*	1.2±0.58*	25.2±5.71*	46.1± 7.05*	49.7± 7.23*	22.1±3.90*	25.2±3.87*
122	14.2±5.30*	1.6±0.64*	20.7±6.77*	53.5± 6.55*	57.5± 6.75*	26.5±3.86*	29.8±3.80*
125	11.7±5.60*	1.6±0.81*	16.8±7.09*	57.2± 5.83*	61.7± 6.29*	28.7±3.17*	32.7±3.69*
130	8.5±3.53*	1.2±0.51*	12.7±4.63*	64.4± 4.58*	68.3± 4.87*	33.8±2.57*	36.7±2.83*
135	5.9±2.02	0.8±0.31*	9.4±2.55*	69.0± 5.12*	72.7± 5.22*	36.9±3.02*	38.9±3.02*
150	4.3±0.85	0.6±0.12*	8.1±1.25*	66.2± 5.23*	69.3± 4.78*	35.0±3.55*	36.3±2.91*
165	4.3±0.68	0.4±0.11*	7.6±1.15	65.4± 6.32*	68.9± 6.37*	35.5±4.00*	35.7±3.63*
180	5.7±1.13	0.4±0.09*	9.2±1.59*	66.3± 6.35*	70.3± 6.63*	34.6±3.83*	35.9±3.80*
195	8.0±2.00*	0.6±0.14*	12.4±2.43*	64.9± 6.50*	68.1± 6.64*	33.0±3.50*	34.2±3.63*
210	8.7±2.21*	0.6±0.14*	13.4±2.68*	64.2± 6.61*	67.8± 6.90*	32.3±3.50*	33.6±3.69*
225	9.2±2.02*	0.7±0.13*	13.8±2.30*	63.5± 6.52*	67.5± 6.88*	31.7±3.39*	33.8±3.70*
240	9.3±1.81*	0.7±0.12*	14.1±2.02*	64.1± 6.93*	68.6± 7.40*	31.1±3.53*	34.1±3.81*

*$p < 0.05$

Table 1--Continued

Δ time	Tp(V)s	Tp(V)m
-5	10.0±1.01	9.3±1.18
0	10.0±1.01	9.3±1.18
15	3.1±0.63*	3.2±0.73*
30	3.8±0.56*	4.1±0.50*
45	4.5±0.93*	4.2±0.67*
60	4.3±1.30*	4.5±0.84*
75	3.7±1.27*	4.7±0.89*
90	3.5±1.11*	4.6±0.87*
105	3.6±1.06*	4.7±0.86*
120	4.0±1.17*	4.7±0.92*
122	5.7±1.46*	6.5±1.10*
125	7.1±1.67*	8.2±1.31
130	9.9±2.41*	10.7±1.64
135	12.2±2.73*	12.3±1.93
150	11.3±1.75*	11.5±1.91
165	11.7±1.73*	10.2±1.89
180	9.5±1.25*	8.2±1.51
195	7.9±0.73*	7.3±0.86
210	7.8±0.77*	6.9±0.77*
225	7.5±0.79*	6.8±0.79*
240	7.0±0.83*	6.5±0.87*

*$p < 0.05$

Table 2. Effect of transfusion (1000 cc whole blood/25 minutes) on saline control animals. Saline was administered 20 cc/10 minutes at minute 0. Transfusion was begun at minute 120. Asterisk denotes statistical significance (difference from time "0" in pre-infusion period) at the $p < 0.05$ level. $N = 7$; limb wt 477.1 ± 13.67 g. Abbreviations correspond to Table 1. Brachial and cephalic veins cut.

Table 2

Δ time	Accum. wt.	A.P.	Pssv	Plsv	Pssa	Fs/100g	Psmv
-5	0.0±0.00	120.0±6.89	12.4±2.48	7.3±1.42	88.0± 9.65	13.4±1.87	8.6±0.81
0	0.0±0.22	120.0±6.89	12.5±2.41	7.3±1.42	88.0± 9.65	13.4±1.87	8.6±0.81
15	-0.6±0.30	118.1±7.48	12.1±2.31	6.6±1.42	86.7±11.00	12.2±1.70	8.6±0.84
30	0.0±0.49	114.6±5.56	12.1±2.23	6.9±1.41	84.4± 8.85	12.3±1.69	8.7±0.94
45	0.1±0.55	115.6±4.88	12.5±2.23	7.1±1.43	84.3± 8.58	12.2±1.64	8.9±0.78
60	0.3±0.68	114.9±4.74	12.2±2.23	7.0±1.42	81.7± 9.02	11.8±1.29	9.0±0.78
75	0.2±0,87	110.6±5.87	11.9±2.15	6.5±1.25	77.9±10.48	11.4±1.17	8.4±0.75
90	0.6±1.11	108.9±6.29	12.5±1.79	6.6±1.04	77.6± 8.34	12.5±1.45	8.3±0.84
105	1.3±1.28	112.6±5.68	12.6±1.62	6.9±0.92	79.0± 8.84	13.3±1.48	8.4±0.72
120	1.7±1.32	117.1±5.76	12.1±1.89	6.6±1.20	80.9± 6.38	13.1±1.71	8.4±0.79
122	2.7±1.25*	120.0±4.90	13.4±2.37	7.3±1.55	82.6± 6.19	13.7±1.81	9.1±0.68
125	4.1±1.16*	127.3±6.30	15.7±2.71	8.9±1.92	85.0± 7.23	15.3±2.49	10.5±0.50*
130	5.9±0.87*	129.7±6.81	18.1±3.31	10.3±2.27	88.0± 7.26	16.4±3.01	11.7±0.75*
135	7.6±1.04*	132.6±6.44	19.3±3.53	11.5±2.49	88.9± 7.28	16.5±2.86	13.2±1.03*
150	10.4±1.36*	135.6±6.40	19.0±3.44	10.6±2.56	89.9± 8.89	14.5±1.41	14.6±1.09*
165	12.4±1.21*	130.0±9.45	17.3±2.84	9.8±2.38	89.9± 8.24	13.7±1.26	12.9±0.84*
180	14.3±1.78*	127.6±7.70	17.1±2.89	9.5±2.09	88.3± 6.15	13.0±1.14	11.9±0.88*
195	15.4±1.73*	126.7±7.38	17.0±2.77	9.2±1.68	96.7± 7.66	12.7±1.23	11.1±0.81*
210	18.1±1.79*	128.3±5.03	17.6±2.44	9.5±1.43	90.9± 4.33	13.5±1.01	10.9±0.56*
225	18.9±1.70*	127.0±4.47	17.4±2.22	9.6±1.47	91.0± 3.41	12.9±0.98	10.7±0.68*
240	19.3±1.61*	126.4±4.81	16.9±2.51	9.3±1.50	92.0± 3.06	12.3±1.10	10.4±0.48*

*$p < 0.05$

Table 2--Continued

Δ time	Plmv	Psma	Fm/100g	Ft/100g	Rap	Rsa	R(s-v)s
-5	5.0±0.58	90.9±6.00	7.9±0.86	21.3±2.07	2.0±0.38	2.3±0.47	6.6±1.38
0	5.0±0.58	90.9±6.00	7.9±0.86	21.3±2.07	2.0±0.38	2.3±0.47	6.6±1.37
15	5.2±0.82	87.9±4.73	7.5±1.11	19.8±1.76	2.0±0.38	2.6±0.56	6.9±1.41
30	5.2±0.76	87.0±3.35	7.5±1.04	19.9±1.83	2.0±0.38	2.5±0.57	6.6±1.27
45	5.0±0.49	87.4±3.14	7.5±1.10	19.7±1.82	2.1±0.35	2.6±0.54	6.6±1.30
60	5.2±0.60	85.6±2.77	7.0±1.09	18.8±1.37	2.1±0.35	2.7±0.48	6.5±1.19
75	5.1±0.71	77.1±4.33	6.5±0.90	17.9±1.19	1.9±0.44	2.8±0.45	6.4±1.45
90	5.1±0.77	83.6±5.20	6.3±0.80	18.9±1.25	1.8±0.39	2.6±0.51	5.6±0.95
105	5.1±0.71	82.1±3.09	6.4±0.74	19.7±1.35	1.8±0.39	2.6±0.50	5.5±0.93
120	5.0±0.66	85.6±4.01	6.5±0.82	19.6±1.89	1.9±0.44	2.8±0.34	5.9±1.06
122	5.6±0.68	86.7±4.84	7.9±1.47	21.6±2.40	2.1±0.46	2.7±0.34	5.8±1.20
125	6.9±0.77*	94.9±6.44	6.2±1.56	21.6±3.63	3.5±0.82	2.8±0.42	5.5±1.23
130	8.1±1.04*	95.6±7.64	7.6±1.39	24.0±3.95	4.9±1.00*	2.7±0.38	5.3±1.27
135	8.8±1.04*	97.7±7.90	8.5±1.32	25.0±3.69	6.5±1.46*	2.7±0.41	5.2±1.27
150	8.7±0.70*	94.7±9.32	8.7±1.45	23.3±2.42	7.9±1.44*	3.1±0.42	5.1±0.97
165	8.2±0.57*	96.4±9.15	8.2±1.28	21.9±2.32	4.6±1.01*	2.9±0.59	5.5±0.85
180	7.9±-.63*	94.3±8.96	7.4±1.10	20.4±2.11	3.6±0.85*	2.9±0.43	5.8±0.91
195	7.6±0.58*	97.6±7.37	6.7±1.29	19.5±2.29	3.5±0.97	2.3±0.42	6.8±1.14
210	7.9±0.75*	98.1±6.84	6.6±1.16	20.1±2.90	3.8±0.75*	2.8±0.41	5.6±0.66
225	7.7±0.76*	99.3±6.63	6.1±1.42	19.0±2.32	4.1±0.66*	2.8±0.41	5.9±0.65
240	7.5±0.61*	98.1±7.04	6.0±1.44	18.3±2.44	4.2±0.68*	2.8±0.42	6.5±0.83

*$p < 0.05$

Table 2--Continued

Δ time	Rsv	Rst	Rma	R(s-v)m	Rmv	Rmt	Rat
-5	0.4±0.09	9.3±1.10	4.0±0.58	11.9±2.34	0.5±0.10	16.4±2.84	1.3±0.19
0	0.4±0.08	9.3±1.10	4.0±0.58	11.9±2.34	0.5±0.10	16.4±2.84	1.3±0.19
15	0.5±0.09	10.0±1.24	5.1±1.33	12.7±2.68	0.5±0.13	18.3±4.04	1.4±0.13
30	0.5±0.09	9.5±1.05	4.5±1.03	12.2±2.24	0.6±0.15	17.2±3.37	1.2±0.17
45	0.5±0.08	9.7±1.05	4.7±1.14	12.3±2.10	0.6±0.14	17.6±3.34	1.3±0.17
60	0.4±0.07	9.7±0.93	5.1±1.10	12.7±2.16	0.6±0.14	18.5±3.29	1.5±0.19
75	0.5±0.08	9.7±1.09	6.1±1.16	12.1±2.06	0.6±0.12	18.8±3.25	1.6±0.20
90	0.5±0.03	8.8±0.91	4.5±1.26	13.4±2.25	0.6±0.13	18.5±3.08	1.5±0.23
105	0.5±0.07	8.5±0.79	5.4±1.11	12.6±1.72	0.6±0.12	18.6±2.89	1.5±0.19
120	0.4±0.05	9.2±0.97	5.7±1.16	13.2±1.79	0.6±0.14	19.5±3.01	1.7±0.14
122	0.5±0.05	9.0±1.04	5.6±1.39	12.0±2.05	0.6±0.18	18.3±3.75	1.6±0.17
125	0.5±0.05	8.7±1.10	4.9±1.30	11.4±2.42	0.5±0.16	16.8±3.76	1.4±0.28
130	0.5±0.07	8.5±1.19	5.6±1.25	12.5±1.61	0.6±0.15	18.7±2.88	1.6±0.17
135	0.5±0.06	8.4±1.11	5.2±1.35	11.4±1.96	0.6±0.15	17.2±3.37	1.5±0.12
150	0.6±0.07*	8.8±0.67	6.0±1.44	10.1±1.25	0.8±0.14	16.9±2.70	1.8±0.21
165	0.5±0.06	8.9±0.57	4.6±0.75	10.8±1.05	0.6±0.24	16.1±1.64	1.6±0.24
180	0.6±0.10*	9.3±0.63	5.0±0.78	11.8±1.22	0.6±0.13	17.4±1.59	1.7±0.21
195	0.6±0.09*	9.7±0.99	5.0±0.90	14.9±2.17	0.6±0.16	20.5±2.70	1.4±0.25
210	0.6±0.09*	9.0±0.51	5.3±0.83	15.2±2.18	0.5±0.14	21.0±2.73	1.6±0.23
225	0.6±0.08*	9.3±0.51	4.2±1.07	12.0±2.56	0.4±0.14	16.6±3.59	1.3±0.33
240	0.6±0.10*	9.8±0.60	4.5±1.20	12.2±2.57	0.4±0.12	17.1±3.73	1.3±0.33

*$p < 0.05$

Table 2--Continued

Δ time	R(s-v)t	Rvt	Rt	Tp(A)s	Tp(A)m	Tp(s-v)s
-5	4.0±0.84	0.2±0.03	5.7±0.71	104.0±8.36	105.4±6.26	50.2±5.31
0	4.0±0.84	0.2±0.03	5.7±0.71	104.0±8.36	105.4±6.26	50.2±5.33
15	4.3±0.83	0.2±0.03	6.1±0.71	102.4±8.80	103.0±5.99	49.4±5.16
30	4.1±0.89	0.2±0.03	5.8±0.90	99.5±6.48	100.8±4.38	48.3±4.04
45	4.1±0.77	0.2±0.03	5.9±0.71	100.0±6.11	101.5±3.86	48.4±3.76
60	4.1±0.78	0.2±0.03	6.1±0.76	98.3±6.32	100.2±3.60	47.0±3.99
75	4.0±0.85	0.2±0.03	6.1±0.72	94.2±7.81	93.9±4.98	44.9±4.83
90	3.8±0.59	0.2±0.04	5.6±0.80	93.2±6.81	96.2±5.31	45.0±3.92
105	3.6±0.53	0.2±0.03	5.5±0.57	95.8±6.46	97.4±4.30	45.8±4.22
120	3.9±0.61	0.2±0.03	6.0±0.45	99.0±5.28	101.4±4.70	46.5±2.77
122	3.7±0.74	0.2±0.03	5.8±0.64	101.3±4.46	103.4±4.66	48.0±2.54
125	3.2±0.93	0.2±0.05	5.0±0.81	106.1±5.25	111.1±6.10	50.4±2.97
130	3.7±0.76	0.2±0.04	5.8±1.12	108.9±5.99	112.6±7.08	53.0±2.89
135	3.5±0.79	0.2±0.03	5.5±0.83	110.7±5.73	115.1±7.06	54.1±2.40
150	3.4±0.56	0.3±0.06*	5.6±0.82	112.7±7.85	115.1±8.59	54.4±3.90
165	3.6±0.48	0.2±0.03	5.6±0.54	109.9±7.88	113.2±9.11	53.6±3.77
180	3.8±0.54	0.2±0.05	6.0±0.36	107.9±6.13	110.9±7.86	52.7±2.53
195	4.5±0.69	0.2±0.05	6.4±0.42	111.7±5.19	112.1±6.60	56.9±1.33
210	4.0±0.49	0.2±0.03	6.2±0.66	109.6±3.75	113.2±5.34	54.2±1.56
225	3.5±0.72	0.2±0.05	5.3±0.97	109.0±2.75	113.1±5.24	54.2±1.17
240	3.7±0.81	0.2±0.05	5.5±1.05	109.2±2.54	112.3±5.63	54.4±1.15

*p 0.05

Table 2--Continued

Δ time	Tp(s-v)m	Tp(v)s	Tp(v)m
-5	49.7±3.19	9.8±1.95	6.8±0.60
0	49.7±3.19	9.9±1.91	6.8±0.60
15	48.2±2.72	9.4±1.85	6.9±0.78
30	47.9±2.06	9.5±1.81	7.0±0.76
45	48.1±1.84	9.8±1.82	7.0±0.56
60	47.3±1.66	9.6±1.81	7.1±0.62
75	42.8±2.50	9.2±1.69	6.7±0.65
90	45.9±2.89	9.6±1.39	6.7±0.77
105	45.3±1.86	9.8±1.25	6.8±0.66
120	47.0±2.17	9.4±1.53	6.7±0.68
122	47.9±2.55	10.4±1.92	7.4±0.62
125	52.7±3.18	12.3±2.29	8.7±0.53*
130	53.6±3.70	14.2±2.75	9.9±0.81*
135	55.5±3.88	15.4±2.98	11.0±0.92*
150	54.6±3.88	14.8±2.93	11.6±0.60*
165	54.6±4.60	13.5±2.56	10.5±0.42*
180	53.1±4.35	13.3±2.40	9.9±0.40*
195	54.4±3.51	13.1±2.11	9.4±0.47*
210	54.5±3.26	13.5±1.83	9.4±0.53*
225	55.0±3.21	13.5±1.76	9.2±0.64*
240	54.3±3.44	13.1±1.90	9.0±0.42*

*$p < 0.05$

Table 3. Effect of transfusion (1000 cc whole blood/25 minutes) on animals previously administered endotoxin (5 mg/Kg/20 cc saline) in a ten-minute infusion. Endotoxin was administered at minute 0. Transfusion began at minute 120. Asterisk denotes statistical significance (difference from time "0" in pre-endotoxin period) at the $p < 0.05$ level. $N = 7$; limb wt. 495.1 ± 19.09 g. Brachial and cephalic veins intact. Abbreviations correspond to Table 1.

Table 3

Δ time	Δ wt.	A.P.	Pssv	Plsv	Pssa	Psmv	Plmv
-5	0.0±0.00	149.0± 3.45	13.4±1.14	7.3±0.90	111.2±6.02	13.7±2.51	6.9±0.76
0	0.3±0.33	149.0± 3.45	13.4±1.14	7.3±0.90	111.2±6.02	13.7±2.51	6.9±0.76
15	-12.4±0.73*	107.4±10.23*	7.3±0.86*	3.5±0.72	93.4±9.69	5.8±0.91	4.3±0.90*
30	-12.4±1.14*	122.3± 4.11*	8.2±0.62*	4.5±0.62	96.2±6.27	7.8±0.96*	5.5±0.86
45	-12.9±1.71*	112.3± 6.10*	8.3±0.72*	4.4±0.63	88.0±4.98*	7.5±1.16*	5.3±1.02
60	-15.9±2.75*	87.4± 9.07*	8.6±1.42*	3.9±0.60	68.7±7.02*	7.1±0.93*	5.2±1.10
75	-17.5±3.24*	75.9± 8.70*	8.6±1.50*	3.9±0.68	57.4±8.28*	6.5±0.73*	4.8±1.12
90	-18.6±4.45*	72.0± 8.80*	8.3±1.44*	4.1±0.62	48.9±8.06*	6.8±0.77*	4.8±1.09
105	-18.9±4.91*	72.9± 8.59*	9.9±1.58	5.3±0.97	48.7±6.75*	7.5±0.88*	5.3±1.09
120	-18.7±5.25*	75.7± 8.67*	10.3±1.58	5.5±1.20	51.8±6.91*	8.0±1.18*	5.8±1.55
122	-17.6±5.08*	83.9± 9.57*	12.9±2.59	7.8±2.51	57.2±6.87*	11.0±1.36	7.8±1.30
125	-15.3±4.79*	98.7± 9.12*	15.4±2.83	9.4±3.19	62.9±6.21*	12.3±1.47	8.7±1.36
130	-13.1±4.15*	103.6± 8.78*	16.3±3.04	9.7±3.18	63.9±6.64*	12.4±1.76	8.8±1.28
135	-10.6±4.09*	107.4± 9.26*	17.3±3.08	10.0±3.55	65.8±6.43*	14.3±1.89	10.1±1.59*
150	- 7.9±4.53*	107.9±13.21*	18.4±2.61*	9.3±2.16	63.3±8.56*	14.6±1.92	9.9±1.10*
165	- 7.6±5.35*	103.1±13.32*	16.7±2.66	8.8±1.60	64.9±8.50*	13.1±1.70	8.8±0.91
180	- 6.4±6.67	102.6±11.98*	15.7±2.31	8.3±1.34	66.4±8.35*	11.9±1.05	8.8±0.78
195	- 7.1±7.89	96.7±10.50*	14.1±1.67	8.0±1.15	65.0±7.68*	10.4±0.65	8.1±0.53
210	- 7.9±7.35	94.6± 9.68*	12.5±1.25	7.3±0.85	63.3±7.14*	9.9±0.64	7.8±0.42
225	- 8.7±7.45	92.7± 9.70*	11.9±1.19	6.8±0.89	62.0±6.85*	9.3±0.64	7.2±0.69
240	- 9.8±7.50*	86.9± 9.42*	10.4±0.95	5.8±0.65	57.0±6.73*	8.4±0.60*	6.5±0.66

*p · 0.05

Table 3--Continued

time	Psma	Rap
-5	115.6±4.62	2.8±0.46
0	115.6±4.62	2.8±0.46
15	93.9±9.48*	0.9±0.32*
30	100.2±4.84	0.9±0.47*
45	92.2±4.71*	1.2±0.58*
60	71.6±8.85*	1.0±0.63*
75	61.5±7.96*	0.5±0.64*
90	53.2±7.77*	0.8±0.76*
105	56.4±7.54*	1.0±0.76*
120	58.3±6.91*	1.0±0.75*
122	66.0±8.50*	1.4±0.61*
125	72.4±6.64*	2.2±0.47
130	75.1±7.23*	2.1±0.42
135	76.1±7.02*	2.8±0.61
150	76.3±11.00*	3.0±1.06
165	74.2±10.48*	1.8±0.60
180	74.6±9.24*	1.9±0.67
195	72.0±7.72*	2.0±0.86
210	69.2±6.82*	1.5±0.69
225	68.5±6.72*	1.5±0.69
240	65.0±6.69*	1.3±0.73

*p · 0.05

Table 4. Effect of transfusion (1000 cc whole blood/25 minutes) on saline control animals. Saline was administered 20 cc/10 minutes at minute 0. Transfusion was begun at minute 120. Asterisk denotes statistical significance (difference from time "0" in pre-infusion period) at the $p < 0.05$ level. $N = 7$; limb wt 492.9 ± 32 g. Abbreviations correspond to Table 1. Brachial and cephalic veins intact.

Table 4

time	wt.	A.P.	Pssv	Plsv	Pssa	Psmv	Plmv
-5	0.0±0.00	144.6±2.62	12.6±0.57	6.2±0.26	118.6± 4.79	9.7±1.15	5.4±0.48
0	0.4±0.30	145.3±2.50	12.6±0.57	6.1±0.26	119.4± 4.33	9.7±1.15	5.4±0.52
15	0.5±0.61	145.4±2.52	12.1±0.70	6.0±0.22	120.7± 3.71	9.9±1.16	5.4±0.48
30	0.9±0.70	144.9±1.96	12.0±0.38	5.9±0.18	120.4± 2.59	9.1±1.06	5.4±0.48
45	1.3±0.84	143.9±1.39	11.6±0.50	5.9±0.18	119.9± 1.96	9.4±1.13	5.6±0.72
60	2.5±1.09*	144.6±1.77	11.6±0.56	5.8±0.35	119.1± 1.79	9.6±1.23	5.8±0.70
75	2.6±1.30*	141.1±1.58	11.7±0.55	6.0±0.26	118.1± 1.68	9.6±1.23	5.7±0.75
90	2.6±1.32*	138.7±1.77	11.6±0.61	5.8±0.24	116.4± 2.17	9.2± 1.22	5.7±0.72
105	2.6±1.31*	137.7±1.94	11.6±0.72	5.7±0.38	116.0± 2.09	9.4±1.23	5.8±0.63
120	2.6±1.30*	139.4±1.46	11.5±0.59	5.5±0.29	118.7± 1.52	9.4±1.25	5.9±0.70
122	4.3±1.07*	149.3±1.70	12.6±0.69	6.3±0.37	121.4± 2.94	10.6±1.11	6.7±0.70
125	6.1±0.85*	152.3±1.86*	13.6±0.86	6.9±0.41	125.9± 3.39	11.0±1.15	7.1±0.76
130	9.1±1.31*	157.7±2.93*	15.8±1.24*	8.3±0.70*	125.2± 5.29	12.3±1.25	8.6±1.02*
135	12.0±1.70*	158.7±3.50*	17.5±1.39*	9.7±0.60*	122.1± 6.88	13.4±1.11*	9.6±0.90*
150	15.7±2.29*	161.1±6.50*	18.9±1.95*	10.7±1.18*	122.3±13.50	14.1±0.77*	10.1±0.89*
165	19.5±2.62*	149.9±4.68	16.5±2.12*	8.1±0.97*	110.7± 8.86	11.4±0.76	7.7±0.89
180	21.8±2.63*	145.9±1.65	15.6±1.44*	7.3±0.55	109.4± 7.51	10.5±0.97	7.3±0.89
195	22.0±2.50*	145.9±2.27	14.5±0.98	7.1±0.52	109.4± 7.43	10.4±0.99	7.0±0.89
210	22.5±2.42*	144.9±3.02	14.1±0.93	7.2±0.34	113.0± 6.43	9.9±0.94	6.9±0.76
225	23.4±2.74*	146.0±3.42	14.1±0.69	7.1±0.32	112.1± 6.22	9.8±0.84	6.7±0.64
240	23.8±3.11*	147.6±3.91	13.8±0.65	7.1±0.32	110.9± 6.08	9.5±0.76	6.6±0.61

*p 0.05

Table 4--Continued

Δ time	Psma	Rap
-5	113.9±6.54	0.3±0.61
0	114.4±6.51	0.2±0.57
15	116.7±5.68	0.2±0.59
30	118.3±4.92	0.1±0.61
45	118.9±4.79	-0.2±0.61
60	116.6±4.83	-0.2±0.61
75	114.9±5.01	-0.1±0.59
90	113.4±5.65	-0.1±0.56
105	114.7±6.02	0.2±0.55
120	115.6±5.51	0.3±0.53
122	119.7±5.63	1.0±0.56
125	123.4±5.79	2.0±0.54*
130	126.4±7.04	3.8±0.55*
135	130.3±9.97	5.2±0.86*
150	125.7±8.59	7.0±1.04*
165	116.4±8.17	3.7±1.63*
180	114.7±6.44	1.1±0.82
195	114.7±6.88	1.2±0.88
210	115.1±7.32	1.6±0.81
225	116.0±7.25	1.5±0.75
240	115.2±6.56	1.6±0.73

*$p < 0.05$

TABLE 5. Effect of transfusion (1000 cc whole blood in 25 minutes) on hematocrits of animals administered endotoxin (5 mg/Kg) at time "0" and saline control animals. (N = 7) Transfusion was begun at minute 120

Time (minutes)	Control Groups	
	Veins Intact	Veins Cut
0	43.6 ± 1.57	42.9 ± 1.42
120	45.7 ± 1.17	45.6 ± 2.17
135	46.1 ± 1.72	49.1 ± 2.32*
240	49.7 ± 2.40*	53.7 ± 2.66*
Time (minutes)	Experimental Groups	
	Veins Intact	Veins Cut
0	43.7 ± 1.36	38.1 ± 2.54
60	48.6 ± 1.62*	41.3 ± 2.93
120	53.4 ± 1.00*	49.6 ± 4.01*
135	53.6 ± 1.04	51.0 ± 3.46*
240	55.7 ± 0.68*	56.9 ± 3.54*

CHAPTER VI

DISCUSSION

Forelimb weight fell rapidly initially (0-15 min.) in response to endotoxin (5 mg/Kg) and then more slowly up to minute 120. Forelimb weight did not change significantly during this time period in saline infused control animals. A continuous fall in forelimb weight following endotoxin administration has been reported in a previous study by the author (61) and by Hinshaw and his co-workers (30). Both utilized the isolated autoperfused canine foreleg preparation. The weight loss is theoretically attributable to a decreased vascular volume, interstitial fluid volume, intracellular fluid volume or some combination of these three factors. The weight loss, during the first 15 minutes, was associated with increases in all segmental vascular resistances. This suggests that mean vascular caliber was decreased, with a consequent decrease of vascular blood volume. From minutes 15 to 120 resistance in all vascular segments, particularly in the capacitance vessels, i.e., small vessels and large veins, increased in skin but declined toward control in skeletal muscle; the net effect being a slight rise (small vessel segment) and a virtual

plateauing (large vein segment) of resistance in the capacitance vessels. These responses suggest that mean vessel caliber was unchanged or somewhat reduced during this period and that forelimb blood volume was also constant or decreasing slightly. It is unlikely then that the large weight loss observed during this period was caused completely by a reduction in vascular volume and probably represented extravascular fluid reabsorption. This is essentially as has been previously reported by the author (61). The response of isolated forelimbs with intact brachial and cephalic veins was essentially the same as that of the limbs in which these vessels were cut, and suggests that the responses observed with the cut vein preparation were not altered by the cannulation of the brachial and cephalic veins or the ligation of the uncannulated ends of these vessels.

Although forelimb weight continuously decreased from minutes 0-120, it is nonetheless still possible that microvascular permeability to plasma proteins increased. Fluid influx could still occur if the transmural hydrostatic pressure gradient fell to a lower level than the transmural colloid osmotic pressure gradient or, if the extracellular-intracellular osmolarity gradient changed in a direction which promoted fluid movement from tissue to blood. However, if microvascular permeability did increase, the increase was

insufficient to casue net fluid efflux, and, in view of the response of the limb to transfusion (minutes 120-240) it is unlikely that microvascular permeability was increased.

It is possible that the observed loss of weight could have been in part influenced by leakage of fluid from the cut ends of lymphatic vessels at the severed end of the limb or by losses of water due to evaporation. As to the latter possibility, all exposed tissues were treated with inert silicon spray to prevent evaporation, hence it is doubtful that evaporation added substantially to the observed weight loss. The weight response in the control animals supports this conclusion. Loss of fluid through lymphatic channels is also unlikely since lymph flow is known to decrease drastically as a result of circulatory shock states and resultant hypotension (62).

After transfusion was begun (min. 120), forelimb weight increased approximately 10 g (min. 120-180) but did not return to pre-endotoxin levels. In control animals a weight gain of approximately 22 g was observed from min. 120 until the end of the experimental period. The weight gain in control animals was associated with significant increases in right atrial pressures, aortic pressure, small vein pressures, and hematocrit, hematocrit may have increased in part due to spontaneous splenic discharge, since increased hematocrits were observed in control animals; however, no change

in segmental vascular resistances occurred. Therefore, this weight gain may be attributed largely to a rise in extravascular fluid volume subsequent to a rise in capillary hydrostatic pressure.

The rise in hematocrit with no change in vascular resistances suggests that mean vessel caliber possibly increased somewhat and that vascular volume may have increased slightly also. The weight gain observed in endotoxin animals (min. 120-180) is theoretically attributable to an increase in vascular volume, to an increase in extravascular fluid volume, or to a combination of these two factors. The weight gain was associated with increases in right atrial pressure, which rose to levels which were not significantly different from pre-endotoxin levels; aortic pressure, which remained below pre-endotoxin levels; small vein pressures, which rose to levels slightly above pre-endotoxin levels; and hematocrit, which was above pre-endotoxin levels. In this case, all segmental vascular resistances decreased. These responses indicate that mean vessel caliber and inferentially vascular volume were increasing during this time. Indeed, total blood flow was observed to increase during this time period. The weight gain which occurred during this period is then largely due to an increased vascular volume subsequent to an increased vascular radius and a fall in segmental vascular resistances.

Although an increase in extravascular fluid volume may have occurred, such an increase was of little significance when compared with that which occurred in saline control animals after transfusion. It is unlikely that microvascular permeability was increased in the limb, since during this period, both small vein pressure in skin and skeletal muscle rose to values above pre-endotoxin levels and although these pressures had risen to relatively high values, inferring that capillary hydrostatic pressure was above pre-endotoxin levels, the weight gain which occurred during this period was significantly less than that which occurred in the control animals.

While forelimb weight climbed continuously from min. 120 to min. 240 in control animals, weight in endotoxin animals, after the transient rise (min. 120-180), declined until the end of the experimental period. The weight loss during this period was associated with a continuous fall in all vascular pressures, blood flows, and a rise in both total skin and total muscle vascular resistances and hematocrit. It is likely then that the weight loss (approximately 5 g) which occurred during this period was largely due to decreased vascular volume, although capillary hydrostatic pressure, as indicated by falling small vein pressures in skin and skeletal muscle, may have been falling at this time. Thus, fluid influx from interstitial and/or

intercellular sites may have contributed to the weight loss, subsequent to a decrease in the transmural hydrostatic pressure gradient below that of the transmural colloid osmotic pressure gradient.

Constriction of all vascular segments contributed to the increases in total skin and muscle segmental vascular resistances. This was especially so in the skin vasculature and is reflected in total vascular resistance, which remained well above corresponding skeletal muscle total resistance from min. 60 throughout the experimental period although marked muscle vascular constriction was observed from minutes 0-45 (Figures 3, 4). These results agree with those previously reported by Weidner et al. in autoperfused canine forelimbs during endotoxin shock (61).

The resistance increases during the first 15 minutes of endotoxin shock can be ascribed both to active changes, i.e., vascular smooth muscle contraction; passive changes, i.e., decreased transmural pressure (Tables 1, 3); and possibly an increased blood viscosity, due to increased hematocrit. The continued increases in skin resistance up to min. 120 can be ascribed to active decreases in vessel caliber, since average transmural pressures and hematocrit were relatively constant. However, muscle total and segmental vascular resistances waned during this period. This decrease of muscle resistance was concurrent with relatively

constant or falling transmural pressures, thus an active dilation must be involved. Since systemic pressure fell from min. 15-20, the vasodilation was probably not due to decreased baroreceptor stimulus. This decline in muscle resistance could have represented a failure of vasoconstrictor nerve activity due to cerebral ischemia, a gradual failure of the local vasoconstrictor mechanisms, or a greater accumulation of vasodilator metabolites, or some combination of the three. Various blood borne substances (7, 8, 44, 45) have been suggested as contributing to this phenomenon and undoubtedly play a role in maintaining muscle vascular resistances at levels which were at or below corresponding skin vascular resistances from minute 60 until minute 240. Among these substances has been suggested serotonin (5 HT) which reportedly increases skin resistances while having little effect on muscle resistances (6), and catecholamines, which when infused systemically at high dose levels, increase skin resistance proportionately more than skeletal muscle resistance (14). Previously reported increases in plasma $[K^+]$, $[H^+]$, and osmolarity support the concept that metabolic vasodilation contributed at least partially to the waning of muscle vascular resistances (17).

All total and segmental vascular resistances were decreased after transfusion from pretransfusion levels and remained below pretransfusion levels until approximately

minute 180, at which time a significant rise was observed in these parameters from approximately minute 180 until minute 240. The transient decreases in vascular resistances following transfusion are associated with greatly increased transmural pressures, and thus can be largely ascribed to passive increases in vessel caliber subsequent to increased vascular volume. The increases in vascular resistances observed from minutes 180-240 are concurrent with falling transmural pressures in skin and muscle small vessel and large vein segments and probably reflect passive decreases in vessel caliber. Transmural pressure in skin and muscle large artery segments were nearly constant during this period and thus the increased resistance in these segments may reflect an active change resulting from contraction of vascular smooth muscle, and subsequent constriction of vessel caliber. Increased blood viscosity as is reflected by increased hematocrit may also play a part in the late increases in resistance (Table 5).

In conclusion, this study supports the author's previous findings that endotoxin shock is associated with marked skin vascular constriction, but lesser muscle vascular constriction (61). The data herein presented provide no evidence for a greater rise in extravascular fluid volume following transfusion in dogs subjected to endotoxin shock than in saline control animals. This study also fails to

support the hypothesis that transvascular fluid efflux into skin and skeletal muscle occurs following transfusion during endotoxin shock. And, infers that if a progressive plasma volume loss occurs subsequent to fluid filtration following transfusion during endotoxin shock states such a loss does not occur in skin or skeletal muscle.

CHAPTER VII

SUMMARY

A study was undertaken to determine if transfusion leads to excessive filtration of vascular fluid and a disproportionate rise in extravascular fluid volume, especially in skin and skeletal muscle, in dogs previously injected with endotoxin relative to that observed in saline control animals. Male mongrel dogs were anesthetized with sodium pentobarbital, and then administered either endotoxin or saline as an i.v. infusion. After two hours these animals were transfused with 1000 ml of cross-matched whole blood. In endotoxin dogs forelimb weight,pressures and blood flows and segmental vascular resistances in the skin and muscle of the collateral-free, innervated, autoperfused forelimb decreased up to min. 120 as previously reported. Following transfusion forelimb weight increased, but failed to return to pre-endotoxin levels. This initial transient weight gain was due largely to increased vascular volume subsequent to a fall in all segmental vascular resistances in the limb.

The study provides no evidence for an excessive fluid loss from the vascular system to the skin and skeletal muscle of the canine forelimb following transfusion during endotoxin shock.

CHAPTER VIII

SPECULATION AND ADVICE FOR FURTHER STUDY

It seems likely to me on the strength of this study, and an earlier work by Weidner et al., that the primary lesion which occurs in endotoxin shock is not related to transvascular fluid efflux into skin or skeletal muscle (61). However, insofar as the canine model of endotoxemia is concerned much work remains to be done with regard to fluid fluxes, specifically extravasation of fluid from blood to tissue in the visceral circulation. Although many studies have been undertaken with respect to the visceral circulation (12, 20, 26, 27, 29, 31, 38, 40), the actual contribution of the splanchnic vascular beds to the alleged fluid loss is not known with certainty. Application of a gravimetric technique employing the use of segmental vascular resistances to a systematic study of the response of the isolated liver, spleen, and large and small intestines to lethal endotoxemia would certainly help to determine if fluid losses into these beds could account for irreversible canine endotoxemia.

Unfortunately the dog is quite atypical of most other species in that the canine model manifests gross

visceral complications, and, thus makes it a less than ideal model for comparison to human bacteremia, since in the human no visceral complications are seen and, indeed, there is no evidence for plasma volume loss (12, 49). Primates, including humans do exhibit hypotension in response to endotoxin though and approximately 70,000 persons die from gram negative bacteremia every year (58). Thus, the need for quantitative data on the subject is warranted.

I suggest two possible areas for study which might provide much potentially valuable hard data with regard to the locus of the central problem at issue in the study, that is the genesis of irreversibility caused by lethal endotoxemia. The first I suggest, since in all forms of irreversible shock, anoxia is thought to be primary in the "vicious cycle" of events that lead to irreversibility and death (3, 4, 49). However, the effect of endotoxin shock on nutritional blood flow has not been definitively examined. The intestine of the primate is the only vascular bed studied to date (25). Endotoxin shock is said to cause a deleterious redistribution of blood flow in the intestine as measured by D_2O extraction (R. R. Rayner et al., Circ. Res., 8:1212, 1960). A greater percentage of blood flow passes through non nutritional channels which do not permit effective exchange of nutrients between blood and tissue. This redistribution of flow is considered to be important

in determining irreversibility (J. T. Gourzis et al., in Shock and Hypotension, ed. L. C. Mills and J. H. Meyer, Grune and Stratton, p. 289, 1965). The consequences of such a deleterious redistribution of blood flow are easily imagined, however evidence in support of this concept is far from conclusive in my opinion since no other vascular beds have been studied. Therefore, a critical and systematic examination of vascular beds other than the small intestine is warranted.

Secondly, there is much evidence to support the concept that all types of circulatory shock render the reticuloendothelial system of the body incapable of clearing circulating endotoxin from the blood, and that this progressive failure of the reticuloendothelial system allows the perpetuation of the "vicious cycle" by allowing an already compromised systemic circulation to be subjected to progressively higher titers of endotoxin (58).

It is possible, through the use of various kinds of pharmacological means, such as the introduction of certain colloid substances into the portal circulation of the splanchnic vascular bed, to render the liver and spleen either hyperactive or hypoactive in terms of their ability to clear colloidal materials from the blood (T. M. Saba, Arch. Int. Med., 126:1031, 1970). In order to assess the relative contribution of the reticuloendothelial system in

preventing irreversibility in lethal endotoxemia. I suggest that the reticuloendothelial system could be rendered either functionally hypoactive or hyperactive, blood levels of endotoxin could be measured over an arbitrary period of time by the limulus lysate method (ibid.), and nutritional blood flow or segmental vascular resistances or other hemodynamic parameters studied to assess the effect that the functional ability of the reticuloendothelial system to rid the blood of endotoxin has upon the severity of lethal endotoxemia insofar as its ability to produce deleterious derangements of the cardiovascular system is concerned.

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APPENDIX

THE PAPPENHEIMER EQUATION FOR DETERMINATION OF CAPILLARY HYDROSTATIC PRESSURE

$$Pc = \frac{\left(\frac{Rv}{Ra}\right)Pa + Pv}{1 + \frac{Rv}{Ra}}$$

In the example cited in the text

$$\left(\frac{Rv}{Ra}\right) = 1;\ Pa = 30;\ Pv = 0$$

$$Pc = \frac{(1)\ 30 + 0}{1 + (1)}$$

$$Pc = 15 \text{ mm Hg}$$

where

Rv = postcapillary resistance

Ra = precapillary resistance

Pa = arterial pressure

Pv = right atrial pressure.