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Vascular and Extravascular Volume Changes Due to Elevated Venous Pressure (38607)

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The measurement of dynamic changes in total tissue volume, blood volume and interstitial volume during variations in hemodynamics has been the subject of much investigation (1–3). One of the most difficult aspects of these studies in the separation of changes in vascular volume from changes in extravascular volume as measured by changes in weight or total tissue volume (plethysmography). This distinction has been attempted by means of simultaneous measurements of total tissue volume changes and vascular volume by indicators (4). This latter approach is complicated by the fact that different indicators give different measures of vascular volume, e.g., red cells $-{}^{51}Cr$ measures a smaller vascular volume than albumin $-{}^{131}I$ (1, 4). The definition of the indicator vascular volume is also complicated by the accessibility of indicators to all parts of the vascular bed. This is exemplified by the inability of red cells to enter many capillaries presumably due to plasma skimming. In instances of partial to intense precapillary vasoconstriction, segments of the vascular bed are closed and indicators do not enter these vessels. This would result in measurement of only the active or circulating part of the vascular volume. Therefore, indicator volume and actual blood volume changes may not be necessarily comparable.

The changes in total tissue volume by plethysmography or by weight changes are considered to have two components (a) vascular volume presumed to be the determinant of the rapid initial part of the recording and (b) capillary fluid transfer presumed to be measured by the later, slow component of the recording. If an independent method for continuously determining the amount of capillary transfer was used simultaneously with changes in total tissue volume (weight or plethysmography) the actual vascular volume change could be obtained by difference. It should also be possible to determine if component one is entirely due to blood volume change and component two is due entirely to capillary fluid transfer. This problem has also been approached by measuring changes in plasma protein concentration (5). Additionally, there has been recent concern as to whether there is a change in compliance which would be a component of the slow segment of the recording (3). This question might be resolved by comparing tissue weight or volume changes with actual amounts of fluid moved by capillary transfer.

Okada and Schwan (6) produced evidence that blood conductivity is a "very accurate index" of hematocrit. Since changes in hematocrit reflect fluid movements into and out of the blood, conductivity changes should be an independent method of measuring changes in trans vascular fluid shifts.

This report compares the volume of fluid filtered from the blood measured by changes in blood conductivity with the changes in total tissue volume (plethysmography) following changes in venous pressure.

Methods. Eighteen healthy mongrel dogs averaging 17 kg in weight were pretreated with 10 mg/kg morphine sulfate and anesthetized with 15 mg/kg sodium pentobarbital. The dogs were splenectomized in order to prevent large spontaneous changes in hematocrit. The muscles just above the elbow of the left forelimb were dissected into groups and ligated, leaving the brachial artery, brachial and cephalic veins, bone and brachial nerve trunks outside the ligatures. The skin flap produced by the exposure of the muscle groups was used as a seal for a volume recorder (plethysmograph) that was air filled and connected to a Statham PR23-2D-300 transducer. The animals were given 10 mg/kg heparin supplemented at 0.5 hr intervals (2 mg/kg). The brachial and cephalic veins

were separately cannulated and the blood from both veins was channeled into a single tube connected to a Starling resistor for controlling venous pressure. The brachial artery was cannulated and perfused from the right femoral artery by means of a Harvard variable-rate pulsatile infusion pump that is pressure independent over the range studied. During the cannulation procedure, blood flow to the forelimb was interrupted for less than one minute. The tubing connecting the brachial and femoral arteries had a sidearm for measuring perfusion pressure. The venous outflow pressure was monitored from a sidearm of the outflow tubing. A constant sample of the venous outflow was withdrawn from another sidearm of the venous outflow tubing through a conductivity cell (Beckman CEL-D) by means of a Holter pump (Model RL175) using a sampling rate equal to one half the venous outflow.

Experiments were performed in the following manner. Blood flow, arterial$_c$ and venous pressure were set so that the isolated forelimb was isovolumetric. Following recording of control conditions the venous pressure was abruptly increased by changing the caliber of the Starling resistance. The venous pressure was maintained for approximately 1 min and then the venous pressure was abruptly decreased to the control level. This procedure was repeated at venous pressures of 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 mmHg. The changes in venous pressure were carried out in the above sequence in some forelimbs and in random order in other forelimbs. Hematocrits were measured at 2-min intervals throughout the experiments.

The total tissue volume change, total vascular volume change and net capillary transfer rate were determined and compared for each step of the experiments. Following an increase in venous pressure there is a relatively rapid increase in tissue volume, generally assumed to be vascular volume change, followed by a gradual but constant positive slope, generally assumed to be capillary transfer. The total vascular volume change was calculated by extrapolating the constant secondary slope back to zero time. The difference between the starting volume and the extrapolated line at zero time was taken as the total vascular volume change (7). The net capillary transfer rate was determined as the rate of change of the constant slow slope.

Changes in blood conductivity were used to independently determine the net capillary transfer of fluid throughout the time-course of the venous pressure changes. Blood conductivity is inversely proportional to change in hematocrit. The conductivity cell was calibrated in terms of changes in fluid content of the blood by initially determining in triplicate the hematocrit of the blood being used to perfuse the forelimb. A 100 ml aliquot of this blood was then pumped through the conductivity cell with the blood being pumped from and returned to the reservoir that was continuously mixed. Following establishment of a stable recording 0.25 ml of plasma was added to the reservoir, the level of conductivity was again recorded. This procedure was repeated to obtain a calibration curve. The hematocrit for each point on the curve was calculated as a proportional change from the originally determined hematocrit. A typical curve is shown in Fig. 1.

The volume of fluid which leaves the vascular compartment during venous pressure elevations was calculated from the conductivity record. Assuming that the arterial inflow hematocrit is constant, the integral of the change in outflow hematocrit (hct) times the flow (Q) gives the volume of fluid leaving the vasculature: $Q \int_o^i ((\text{hct})_A - (\text{hct})_V)/dt(\text{hct})_V$ where $(\text{hct})_A$ and $(\text{hct})_V$ are the arterial and venous hematocrits respectively, o is the point of venous pressure elevation and i is any point on the curve. For purposes of comparison with the total limb volume change, i was first taken as the point corresponding to the slope change in the conductivity curve after which a new steady state hematocrit is reached. This point also corresponded to the slope change in the plethysmograph record which classically demarks the beginning of the filtration slope and the end of any compliance changes. The integration was next carried out for the remainder of

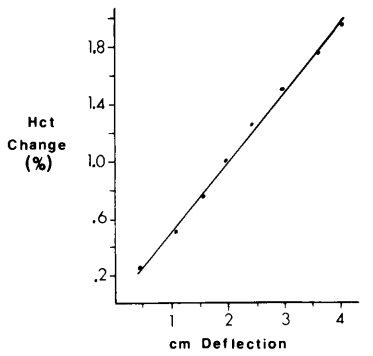

FIG. 1. Plot of conductivity cell calibration as percentage change in hematocrit per mm change in recorder tracing.

the period of venous pressure elevation. The resulting volume per unit time of this portion of the curve is the steady state filtration rate. The amount of catheter delay from the venous tubing to the conductivity cell was determined by injection of a small amount of plasma at the point of venous cannulation and time required for deflection of the conductivity recording was used for locating simultaneous points on the conductivity and plethysmograph records.

The algebraic sum of the total tissue volume and the net capillary transfer of fluid should equal the vascular volume change. Therefore, the vascular volume change would be calculated by the following relationship:

$$V\Delta V = V\Delta T - V\Delta F$$

where $V\Delta V$ = vascular volume change, $V\Delta T$ = total tissue volume change and $V\Delta F$ = volume of fluid transferred across the capillary membrane.

The effluent blood was collected in a graduated cylinder and flow was expressed as milliliters per minute. Inflow was also monitored with a Statham K-2000 flowmeter to verify constancy of flow into the leg.

The arterial perfusion pressure, inflo ', plethysmographic volume changes and blood conductivity changes were recorded on an Electronics for Medicine oscillographic recorder. Statham transducers were used for measuring the pressures.

Forelimb blood flow resistance was calculated as:

$$R = {}^{P}A - {}^{P}V/Q$$

where: R = resistance, ${}^{P}A$ = arterial perfusion pressure, ${}^{P}V$ = venous pressure, and Q = blood flow.

Related values were compared using analysis of variance and Duncan's new multiple-range test. In appropriate cases a paired t test was also applied.

Results. Hemodynamic changes. Eighteen dog forelimbs averaging 584 ± 13g in weight were perfused at an average blood flow rate of 59 ± 3.8 ml/min. The control venous outflow pressure averaged 1.2 ± 0.8 mmHg and the control perfusion pressure averaged 132 ± 20.7 mmHg. The calculated control blood flow resistance averaged 2.24 ± 0.59. The effects of elevating the venous pressure by 5–50 mm Hg above the control level on the arterial perfusion pressure, and blood flow resistance are shown in Table I. It should be noted that as the venous pressure increments became larger the arterial pressure increments were increasingly larger and the calculated blood flow resistance decreased as the venous pressure changes increased in magnitude.

Volume changes. Figure 2 shows a typical recording of changes in total tissue volume (plethysmograph) and changes in blood conductivity following an increment in venous pressure of 20 mm Hg.

It should be noted that there was a rapid increase in total tissue volume concurrent with a marked decrease in blood conductivity. This was followed by a gradual constant increase in total tissue volume which was concurrent with a constant level of blood conductivity significantly below the control level.

Figure 3 shows the changes in total tissue volume from the time of venous pressure increase to the point on the plethysmograph record when the gradual slope is established. The change in volume increased with increasing increments in venous pressure to 40 mm Hg venous pressure change. The changes in volume with the 45 and 50 mm Hg venous pressure changes were progressively

TABLE 1. CHANGES IN ARTERIAL PERFUSION PRESSURE AND BLOOD FLOW RESISTANCE RESULTING FROM ELEVATIONS OF VENOUS PRESSURE IN DOG FORELIMBS.

Venous pressure elevation	Perfusion pressure change		Resistance Change	
(mmHg)	(mmHg)	%	(PRU)	%
5	+2	+1.5	−0.04	−2.2
10	+4	+3.2	−0.07	−3.4
15	+7	+5.2	−0.13	−5.3
20	+11	+8.6	−0.15	−7.7
25	+13	+9.0	−0.20	−7.9
30	+16	+11.8	−0.23	−10.0
35	+20	+15.7	−0.25	−11.0
40	+24	+17.3	−0.27	−13.7
45	+26	+18.8	−0.31	−15.0
50	+28	+18.6	−0.37	−14.2

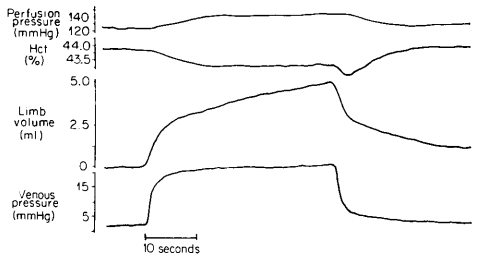

FIG. 2. Tracing of actual record of changes in arterial perfusion pressure, blood conductivity and total limb volume (plethysmography) when the venous outflow pressure is elevated 20 mmHg above control and subsequently returned to control. Blood flow was 59 ml/min. The blood conductivity tracing was shifted to the right to compensate for tubing transit time (see text).

less than the change at 40 mm Hg. When the initial change in volume was corrected by extrapolation of the gradual second slope to zero time the changes in tissue volume followed the same general pattern as the uncorrected volumes except at a lower value.

The volume of fluid lost from the blood as determined from changes in blood conductivity during the initial phase of the response to increases in venous pressure are also shown in Fig. 3. It should be noted that the amount of fluid moved from the blood into the tissue increased in an essentially linear manner to 40 mm Hg venous pressure. The volume of fluid filtered at 40 and 50 mm Hg was not significantly different from that at the 40 mm Hg venous pressure change.

However, the amount of fluid filtered, as measured from the blood conductivity alterations, was approximately 10% of the volume change measured by plethysmography. It is also important that the amount of fluid filtered, as measured from the conductivity changes, was significantly less than the amount filtered as measured by the difference between the uncorrected and corrected initial volume change from the plethysmograph record.

The changes in total tissue volume following increases in venous pressure during the second part of the plethysmograph record are shown in Fig. 4 expressed as ml/min. Also the amount of fluid removed from the blood as determined by the blood conductivity level is shown as ml/min. It should be noted that both measures of fluid volume change increased in an essentially linear manner and both measured the same increments in volume as there was no statistical differences between the values at any change in venous pressure.

Following the return of the venous pressure to control levels (Fig. 2) there was a transient but marked secondary decrease in conductivity lasting several seconds and then the conductivity increased finally reaching control levels. The magnitude of this secondary decrease in conductivity increased with the magnitude of the venous pressure elevation.

Discussion. It has been assumed for some years that the changes in total tissue volume as measured by the plethysmograph or by weight changes were of two components, (a) an initial rapid change generally considered to be due primarily to changes in vascular volume and (b) a later constant slope considered to be due to net capillary movement of fluid. It has been a common procedure to correct the initial volume change for net capillary transfer by extrapolation of the filtration slope back through the initial period to obtain quantitative changes in vascular volume.

In this report an independent measure of

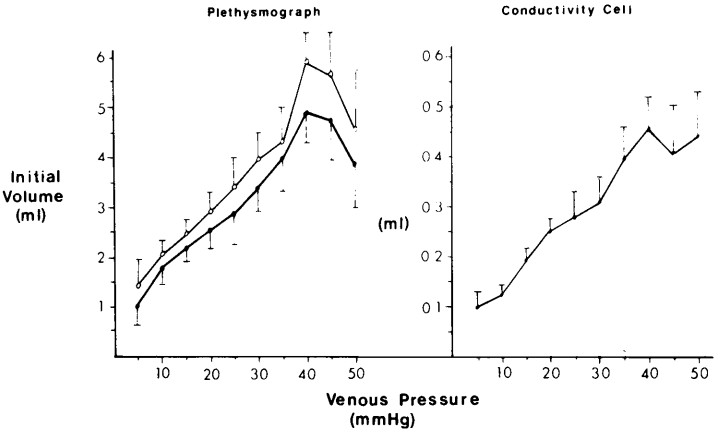

FIG. 3. Left Panel: Changes in total tissue volume during component I of the plethysmograph recording (O——O) and corrected for transcapillary movement of fluids during component II (●——●). Right Panel: Net transcapillary fluid loss during component I as determined from changes in blood conductivity. Brackets indicate I-SEM.

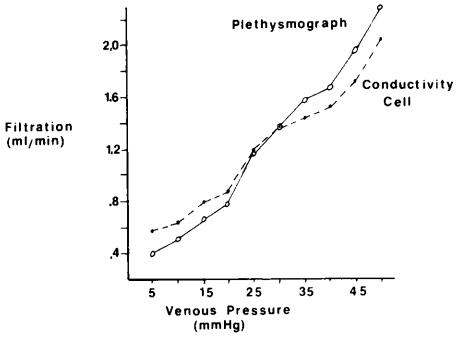

FIG. 4. Changes in total tissue volume (plethysmography) and amount of fluid removed from the blood as determined by blood conductivity changes during component II of the plethysmography record.

the net filtration of fluid was used to assess quantitatively how much of the initial volume change by plethysmography was due to net capillary transfer of fluid. The changes in blood conductivity were continuously monitored concurrent with changes in total tissue volume by plethysmography subsequent to elevations of venous pressure over a range of 5–50 mm Hg.

The data in this report indicate that the initial portion of the tissue volume change has two components, vascular volume change and net capillary transfer of fluid from the blood to the extravascular space. This statement is supported by the data that there is a significant change in blood conductivity reflecting movement of fluid concurrent with the increase in total tissue volume. The data indicate that the greater the change in venous pressure the larger is the volume of fluid transferred from the intra- to the extravascular space. It is however, interesting to note that the amount of fluid transfer is essentially a constant fraction of the total tissue volume change, e.g., 10%.

It should also be noted that the technique of extrapolation for correcting the initial tissue volume change for capillary filtration is not a truly accurate means of obtaining the vascular volume change. The extrapolation technique tends to overestimate the capillary filtration component and, therefore, underestimates the change in vascular volume.

It has been reported by Diana (3) that there is a significant capillary filtration component and our data supports this finding. This was also alluded to by Fronek (8) and Friedman (5).

It is also significant that the total tissue volume change and the rate of loss of fluid from the blood into the extravascular space as measured from the blood conductivity recording were quantitatively the same. If there had been a delayed compliance of the venous system as a result of the elevation of venous pressure it would be expected that

the rate of change of total tissue volume would exceed the rate of capillary filtration. It would, therefore, be reasonable to conclude that the second phase of the plethysmograph record is an accurate measure of the rate of net capillary filtration.

The changes in conductivity noted upon return of the venous pressure to control levels would seem to be the result of the washout of blood from which a significantly large amount of fluid had been removed. It has been reported previously (9) that following elevation of venous pressure a segment of the vascular bed is closed off presumably by a myogenic response of precapillary vessels leaving areas that contain capillaries and venules with sequestered blood. This finding was based on the changes in vascular volume as determined by labeled red cells and albumin. If this is the case in these experiments, and this does appear to be the case, it would seem reasonable to conclude that since these areas containing sequestered blood are continuous with the venous outflow channel that elevation of the venous outflow pressure would elevate the pressure in these sequestered vessels as well as the patent vessels. There would then be a marked outward filtration of fluid from these vessels concentrating the red cells. When the venous pressure is returned to control, these vessels become patent and the sequestered blood is washed out in a sort of bolus.

Summary. Abrupt elevation of venous pressure causes an initial rapid and a secondary slow increase in total tissue volume (plethysmography). Changes in total tissue volume and blood conductivity from the isovolumetric state were determined to assess what factors determined the two components of the tissue volume change. The initial component of the plethysmograph record would appear to be 90% vascular volume change and 10% extravascular volume change. Since the two techniques measured identical amounts of capillary filtration during the second component of the recording there would seem to be no slow component of vascular volume increase following venous pressure elevation. Evidence that elevation of venous pressure causes myogenic closure of precapillary vessels isolating a segment of the microvasculature is presented.

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