SUMMARY On the basis of an electrical analog, open circuit impedance functions were used to analyze the microcirculation. No specific structure need be assumed except a two-port, two-terminal network in which the major artery and vein supplying the tissue represent the input port and the two ends of the microvessel under study are the output port. The open circuit measurements were made by occluding microvessels in the exteriorized omentum of anesthetized rabbits. The pressure upstream and downstream to the occlusion defines the source pressure of a Thévenin's equivalent circuit. The equivalent resistance value was calculated by plotting the flow through a given microvessel against the pressure developed during a gradual occlusion. The changes in pressure vs. the changes in flow during a progressive occlusion were found to be linearly related. The Thévenin's equivalent resistance was maximum downstream to an occluded artery and upstream to the occluded vein. Within the capillary network, source pressures consistently were within a narrow range. Topically applied norepinephrine resulted in marked changes in source resistance and no changes in source pressures. Threshold doses of norepinephrine given intravenously resulted in changes in source pressures, but minimal changes in source resistance, even though a substantial change in vascular resistance was indicated when calculated on the basis of arterial pressure minus micropressure divided by microvessel flow. The present method defines the functional characteristics of the distributing vessels in terms of two pressures and two equivalent resistances and is relatively easy to perform. The technique can be used to determine the vascular components involved in the response to particular stimuli.

PRESSURE-FLOW relationships across discrete organs or masses of tissue usually are described by a lumped numerical expression representing the effective resistance encountered by the blood during its passage from artery to vein. A more precise description of the functional organization of the system would be feasible if the resistance in specific segments of the vascular tree could be measured. Pressure and flow interactions at the tissue level are difficult to formulate because of the complex structural organization of the microvascular network. An especially formi...

A Method for Determining Segmental Resistances in the Microcirculation from Pressure-Flow Measurements

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reconstructions of the network for particular tissues.\textsuperscript{4,5} What was lacking, however, was the ability to analyze pressure-flow relationships in response to particular stimuli.

The present report deals with the application of the methods of electrical circuit network analysis to the microcirculation. For this purpose, no specific structure need be assumed other than a general two-terminal network in which the major artery and vein comprise the input terminals and the arteriolar and venular ends of the microvascular segment under study comprise the output terminals (see circuit diagram in Fig. 1). The method allows one to obtain an estimate of the resistance for the overall tissue flow, which then can be broken down into subfractions representing the three major divisions of the tissue circulation, arteriolar resistance, microcirculatory resistance, and venular resistance.

**Methods**

The analysis was made on the microcirculation in the rabbit omentum by the direct observational method. The tissue was exteriorized under either sodium pentobarbital anesthesia (30 mg/kg, iv) or a short-acting thiobarbiturate, Inactin (40 mg/kg, iv), and kept at body temperature (30°C) with the aid of Ringer-gelatin irrigation.\textsuperscript{6} Routine measurements were made of systemic arterial pressure, central venous pressure, local micropressure (as indicated), vessel diameter by an electronic image-shearing procedure,\textsuperscript{7} and red blood cell velocity by a two-diode procedure.\textsuperscript{8}

An electrical null servosystem\textsuperscript{9} for micropressure recording was used to map the pressure drop across successive segments of the microcirculation. Under steady state conditions there was no positive correlation between the central arterial pressure in different animals and the pressure in microvessels below 50 μm in width;\textsuperscript{10} this clearly indicates some form of vascular adjustment proximal to the arterioles.

Velocity was measured by placing two closely spaced diodes along the longitudinal axis of a small blood vessel and using a cross-correlator to detect the delay time for the passage of red blood cell masses across the two points.\textsuperscript{9} At the effective magnification used, each diode covers a circular area approximately 4 μm in diameter and occupies about half of the vessel diameter for vessels of 20-30 μm and about 25% of the vessel lumen in vessels of 30-50 μm.

There is some uncertainty about how to treat the velocity data to calculate volume-flow rates. The relationship between center line velocity and bulk or mean velocity (cells plus plasma) has been examined in vitro in glass tubes by Baker and Wayland.\textsuperscript{11} For vessel internal diameters of about 30 μm they found that spatial averaging of the photometric signals across the depth of the vessel results in a ratio of center line velocity to mean velocity of 1.6. Some of our data show a comparable relationship; others do not, in particular for vessels in the 20-μm range and below.\textsuperscript{12} A correction factor between center line velocity and mean velocity has yet to be defined for small venules. It is probable that center line to mean velocity ratios may fall below 1.6 and approach 1.0 when single file movement of red cells is present. To avoid a bias in the data we have elected to use the measured velocity data without correction for calculations of flow and resistance. Inasmuch as we are primarily interested in relative changes in these parameters from one microvascular segment to another, we believe that no significant errors are introduced that cannot be corrected when more precise corrections do become available.

Pressure-flow relationships for a whole organ can be dealt with in a relatively straightforward way. One is concerned here with a one-terminal-pair network (Fig. 1A) which has, in most cases, no internal sources. The only requirement, therefore, is to investigate the relationship between the two variables (driving pressure and flow). An assumption of linearity is usually made in order to allow the relationship between pressure and flow to be expressed in peripheral resistance units.

At the level of the microcirculation boundary conditions are set up so that a segment or a microvessel is excluded from the rest of the system; this converts a one-terminal-pair network into a two-terminal-pair network (Fig. 1B) and thus increases the number of parameters needed to describe the system. Two pressures and two flows are identified from which, for a linear system, one can derive six possible network functions that connect each of the four nodes (comprising the two-terminal pairs) to every other node in the network. In practice, however, only three of these network functions need be specified to describe the characteristics of the entire network.

**NETWORK ANALYSIS BY MICRO-OCLUSION PROCEDURE**

A special class of resistance and admittance functions are widely used in network analysis: the open circuit impedance and the short circuit admittance functions.\textsuperscript{13} This type of analysis can be carried out for the microvascular network in several ways. Either flow (Q) can be related to pressure (P) using Equation 1 (conductance or admittance), or one can reverse the analysis and relate pressure (P) to flow (Q) using Equation 2 (resistance or impedance):

\[
\begin{align*}
Q_1 &= Y_{11} P_1 + Y_{12} P_2 \\
Q_2 &= Y_{21} P_1 + Y_{22} P_2
\end{align*}
\]

(Fig. 1)
where the Y values are a short circuit admittance, or
\[ Y = \frac{P}{Q} \]
where the Z values are open circuit resistances. In classical physics, the symbol Z denotes the overall impedance of a system. Thus, an impedance \( Z^e \) consists of a resistive and a reactive component, \( R \) and \( X_j \), so that in equation form
\[ Z^e = R + jX. \]

The data collected for the present studies are only for low frequencies so that the reactive component \( X_n \) is negligible. The equivalent network described is one that responds to changes in average pressure, and pulsatile components are ignored. To avoid confusion in this presentation \( Z_n \), will be referred to as the total vascular resistance for the tissue as a whole.

It would be difficult to develop an equivalent to a short circuit (pressure = 0) in the microcirculation; however, the open circuit equivalent (flow = 0) is comparatively simple to produce by mechanical occlusion of a particular vessel with a microneedle. For this reason, we have used the open circuit resistance functions to describe the microvascular system. It is apparent that, for some tissue preparations, a different network function might lend itself more readily to investigation.

Measurements of this kind can be made in any tissue exposed for intravital microscopy; the intestinal mesentery and omentum are especially well suited because of their thinness and the diversity of microvessels available. The selection of a vessel for this type of analysis requires only that the measured flow be much less than the total flow to the tissue. In the case of the microcirculation, this demand is met by at least several orders of magnitude.

The interruption of flow in any of these small vessels does not significantly disturb input flow or pressure. Thus, \( Z_n \) is identical to the input resistance measured by whole organ studies and is defined by the ratio of arterial pressure minus venous pressure divided by arterial flow. The output resistance, \( Z_{22v} \), in electrical terms is the Thévenins equivalent resistance. The Thévenins theorem is a general transformation which reduces any combination of active or passive linear elements to a simple equivalent network consisting of a pressure source in series with an equivalent passive element (Fig. 2A).

The source pressure is that measured across an open circuit or, in its present application, that developed across an occluded microvessel. A resistance term can then be calculated by plotting the flow through a given microvessel against the pressure developed across a variable resistance. The application to the microvascular system can be modeled by a circuit similar to that shown in Figure 2B. For this purpose, the Thévenins equivalent resistance can be separated into two components, an upstream and a downstream resistance. The pressures that were recorded above and below the site of occlusion are represented individually instead of as a pressure difference. For this general network, \( R_{upstream} + R_{downstream} = Z_{22v} \). Since it is necessary to define the characteristics not only of the network which supplies, but also that which drains a particular microvessel, the following parameters should be known: systemic blood pressure, central venous pressure, flow through the total microvascular bed in the tissue, and the immediately upstream and downstream pressures together with microvascular flow. All of these parameters can be obtained routinely except for total flow through the organ as a whole. As indicated later in the present analysis, this measurement would be needed only to obtain \( Z_n \), total resistance, in absolute terms.

Figure 3 depicts an equivalent network in which are illustrated the distribution and definition of the various parameters that can be studied by the micro-occlusion method. It should be emphasized that we are dealing with an equivalent network. Since measurements of pressure and flow on the input side were routinely carried out on arterioles between 20 and 40 /\mu\text{m} in diameter, \( R_0 \) refers to arterial vessels just proximal to them. In a similar way, since pressure and flow were recorded in postcapillary venular confluences ranging between 20 and 40 /\mu\text{m} in diameter, \( R_0 \) values refer to the downstream venules into which these postcapillaries drain.

Interposed between the above two reference sites is the microvascular network proper, for which the term \( R_{mc} \) is used. The precise portion of the terminal vascular bed included in \( R_{mc} \) will depend on the location of the microvessels selected for the direct measurement of pressure and flow.

When a given subsegment of the microcirculation is mechanically obstructed and blood flow is brought to zero,
the proximal and distal ends of the occluded vessels remain open, respectively, to the upstream (P_u) or downstream (P_d) pressures. P_u and P_d are in an operational sense the reference pressures that determine the flow in that particular vessel. Although the micro-occlusion procedure provides numerical values for reference pressures only, their anatomical location can be more precisely approximated by projecting these values onto our detailed distribution plots of pressure vs. vessel size.

By definition, the vascular resistance for the entire vascular network in a tissue (Z,,) is made up of a series of resistive circuits, an arterial portion (a), a venous portion (v), and the intervening network between the two (me), or

\[ Z_{11} = R_a + R_{mc} + R_v. \] (4)

Since the pressure both upstream and downstream to the occlusion site can be monitored continuously during the period when flow is slowed and brought to a complete stop, the slopes of the dP/dQ plots can be used to calculate the local resistance above and below the observation site. The local resistance (Z_{22}) for any given microvessel is always much higher than Z_{21} or Z_{12} and can be represented as

\[ Z_{22} = R_u + R_d. \] (5)

where R_u is the local resistance above and R_d that below the microvessel. It should be emphasized that R_u and R_d include only a small contiguous portion of the extensive network which makes up R_{mc}. The portion of the network included in R_u and R_d will depend on the location of the vessel selected.

In view of the interlocking nature of the terminal vascular bed, the various resistances that make up the vascular circuit can be expressed as a fraction of the total resistance (Z_{11}) rather than in absolute terms. Thus, microcirculatory resistance (R_{mc}) is expressed as R_{mc}/Z_{11}. This ratio can readily be determined since

\[ R_{mc} = \frac{P_u - P_d}{Z_{11}}. \] (6)

and

\[ Z_{11} = \frac{P_u - P_v}{Q_1}. \] (7)

Since P_v (central venous pressure) is close to zero, the systemic blood pressure (P_A) can be used as the central reference pressure P_1, so that

\[ Z_{11} = \frac{P_1}{Q_1}. \] (8)

Microcirculatory resistance is thus calculated from the expression

\[ R_{mc} = \frac{P_u - P_d}{P_1}. \] (9)

R_u and R_v are likewise expressed as a fraction of the total resistance (Z_{11}) on the basis of the reference pressures upstream and downstream to the occlusion site. Thus,

\[ \frac{R_u}{Z_{11}} = \frac{P_u - P_v}{P_A - P_v} = \frac{P_u}{P_1}. \] (10)

and

\[ \frac{R_v}{Z_{11}} = \frac{P_A - P_v}{P_A - P_d} = 1 - \frac{P_d}{P_1}. \] (11)

The following is an outline of the procedure that was used routinely:

1. Select a terminal arteriole and a venule in the same network which have similar volume-flow rates.
2. Insert a micropipette into the terminal arteriole and the venule for direct recording of pressure.
3. Measure also the velocity at these two points.
4. Obstruct the arteriole downstream below the micropipette, leaving the vessel open to the arterial side of the circulation. Record P_u when flow is stopped and at several intermediate P-Q points during the slowing and reopening of the circulation in the affected vessel.
5. Repeat the obstruction procedure upstream of the pipette, leaving the vessel open to the precapillary and capillary portion of the network. Obtain P_u and intermediate dP/dQ values.
6. Repeat upstream and downstream occlusion in a venule with a corresponding blood flow.
7. Calculate R_u, R_{mc}, and R_v from Equations 9, 10, and 11, using P_u, P_v, and central blood pressure, P_A.
8. Calculate R_u and R_v as reciprocals of dP/dQ slopes.

Results

SEGMENTAL RESISTANCES FOLLOWING MICRO-OCCCLUSION

Two protocols (Fig. 4) are given to demonstrate the distinctive patterns of pressure-flow relationship which are brought out by the micro-occlusion procedure in different portions of the microvascular network.

The intervention is confined to a single microvessel, and there are no changes in the remainder of the microvascular network so that the resulting perturbation of pressure and flow is a purely passive phenomenon which shows a linear relationship.
FIGURE 5 Pressure-flow relationship using rapid micro-occlusion method; rapid transient in different-sized vessels. Pressure-flow points are shown for steady state and for the fully occluded condition. Linear nature of dP/dQ relationship allows rapid determination of \( R_u \) and \( R_d \) for representative microvessels. Open circles are for downstream occlusion run, and solid circles for upstream maneuver. \( R_u \) arteriole and \( R_d \) venule are measures of same network seen from opposite ends of circuit and are expressed as mm Hg/10^{-3} mm^3/sec. Note similarity of runs for arteriole and venule (mirror image).

Each point is a computer readout of a continuously updated average for 3 seconds in which data are simultaneously added and subtracted from the calculation. The system permits the discrimination of 50-100 points during the occlusion procedure, but only a sufficient number are included here to substantiate the linear nature of the pressure-flow regression line. In Figure 5, dP/dQ values are shown for a 27-\( \mu \)m arteriole and for a 43-\( \mu \)m venule. Note that \( R_u \) for the arteriole and \( R_d \) for the venule are essentially the same since they reflect the same segment of the microcirculation.

The method was found to give highly reproducible results. When the micro-obstruction procedure was repeated three or four times, the \( R_u \) or \( R_d \) slopes in each case were almost identical. The actual pressure intercept at zero flow was found to vary at most by only \( \pm 2.5 \) mm Hg. The validity of the method is further supported by the fact that \( P_u \), the upstream reference pressure for an arteriole, and that for its corresponding venule are identical (in the protocol shown, 50 mm Hg). The data indicate the presence of high resistance vein to vein interconnections so that an occluded vein decreases blood flow through the microvascular segment by the same percentage as an occluded arteriole.

In view of the linear nature of the dP/dQ relationship for a given vessel, it was possible to use only two points to develop a set of upstream and downstream plots—the steady state reading and the pressure relationship prevailing under zero flow conditions following rapid occlusion of the vessel (2-3 seconds). In Figure 5 are representative protocols for an arteriole, a precapillary vessel, and a venule, respectively. The plots for the arteriole and venule are essentially mirror images. Successive branchings of the terminal arterioles are characterized by a substantial drop in pressure as the blood stream is directed into the capillary network. This feature is reflected by the comparatively high downstream resistance (\( R_d = 9.2 \) mm Hg/10^{-3} mm^3/sec) in contrast to the low upstream resistance (\( R_u = 1.8 \)). As would be anticipated, \( R_u \) and \( R_d \) become progressively higher when the measuring site lies within the capillary network proper. In these locations the resistance on either side of the capillary tends to become more nearly equal as exemplified by the slopes of the regression lines in the middle plot. Micro-occlusion measurements on vessels in the converging effluent portion of the network show \( R_u \), the resistance on the input side, to be high in contrast to \( R_d \), the resistance on the outflow side of the venule.

The progressive change in conductance from arteriole to precapillary to capillary is strikingly demonstrated (Fig. 6) when \( R_u \) and \( R_d \) relations are plotted separately for vessels of different sizes. The reciprocal of the slope of the dP/dQ line represents the resistance in the vascular segment between the reference pressure (pressure at zero flow) and the point where P and Q are being measured directly. It can be seen that the set of dP/dQ lines which correspond to \( R_u \), the resistance which is encountered in successive segments of the terminal vascular bed proper, pass through a common venous pressure reference point. In all probability this reflects the extensive interanastomosis between these vessels. \( R_u \) increases more than 20-fold from a value of 0.82 in the 39- to 48-\( \mu \)m arterioles to 18 mm Hg/10^{-3} mm^3 per sec in 16-\( \mu \)m precapillaries. Although the pressure in the successive precapillary vessels falls only

FIGURE 6 Comparison of upstream and downstream resistances in progressively smaller precapillary vessels. Change in slope for \( R_u \) reflects the marked increase in resistance in smallest vessels.
from 52 to 35 mm Hg, blood flow falls from $38 \times 10^{-3}$ mm$^3$ per sec to $1 \times 10^{-3}$ mm$^3$ per sec.

On the right (Fig. 6) are shown the corresponding upstream values. In contrast, the $P_a$ values in each of these experiments differ in proportion to the $\Delta P$ between the four vessels for which data were plotted. For example, as the measuring site is moved from a 48-$\mu m$ vessel to a 30-$\mu m$ branch the $P_a$ intercept is 52 mm Hg, which is essentially the pressure of the 48-$\mu m$ vessel from which this branch originated.

In addition to a direct comparison of local resistances, it is possible to calculate the fraction of the total resistance for the vascular circuit as a whole which is contributed by the arterial side of the capillary network and $R_u$ for comparable vessels (on the basis of flow) on the venous side are measurements of the same intervening segment of the microcirculation. When a venule is obstructed below the point of pressure measurement, one is looking back into the capillary bed and measuring the resistance characteristics of the network from which blood is being collected. Conversely, when the corresponding arteriole is obstructed above the site of pressure measurement, one is looking down into the same network. As indicated by the

**Table 1** Arterioles in Rabbit Omentum

<table>
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<th>Diam (µm)</th>
<th>P_{ox} (mm Hg)</th>
<th>Q_{ox}</th>
<th>P_a (mm Hg)</th>
<th>P_d (mm Hg)</th>
<th>$R_u$</th>
<th>$R_d$</th>
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<th>$R_s$</th>
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</table>

\(n\) = number of measurements; sbv = small blood vessels; other abbreviations are defined in the text.

\(\ast\) 10^{-2} mm$^3$/sec.

\(\dagger\) mm Hg/10^{-3} mm$^3$ per sec.

**DISTRIBUTION OF MICROVASCULAR RESISTANCES**

Figure 7 shows a log-log plot of the distribution of $R_u$ and $R_d$ values for vessels on the arterial and venous sides of the microvascular network in the omentum. The $R_u$ and $R_d$ values are an average of almost 200 separate measurements for vessels ranging from 100 to 15 $\mu m$ in width, and include arterioles, precapillaries, postcapillaries, and venules. The successive segments are categorized on the basis of the progressive reduction in volumetric flow rates. The plot graphically reinforces a point that has been raised several times, namely, that $R_d$ for the vessels on the arterial side of the capillary network and $R_u$ for comparable vessels (on the basis of flow) on the venous side are measurements of the same intervening segment of the microcirculation. When a venule is obstructed below the point of pressure measurement, in essence one is looking back into the capillary bed and measuring the resistance characteristics of the network from which blood is being collected. Conversely, when the corresponding arteriole is obstructed above the site of pressure measurement, one is looking down into the same network. As indicated by the
slopes of the two lines, the two values are usually quite close. In some instances capillary resistance is found to be somewhat lower when measured from the venular side, presumably because of the presence of numerous venular collaterals on the venous side of the network.

The regression lines shown are a composite of in series and parallel resistances, and their actual slope will depend on whether the resistance in successive segments is increasing more rapidly than the rate at which blood flow is dropping. The change in resistance is related to the size of the vessel and as shown follows a power law function $A Q^B$, with the exponent $B$ differing somewhat for upstream and downstream $R$ plots. Whether $B$ is greater than or smaller than 1 will depend on a number of factors ranging from the geometry of the network, the flow properties of the blood, hematocrit distribution, to interarcading connections, etc. $A$ and $B$ are parameters in an empirical equation which summarizes the flow-resistance relationship. In the microcirculation, the pressure differentials measured in these experiments fall within a comparatively narrow range, whereas flow varied by more than a factor of 1,000. The absolute resistance thus depends to a large extent on the flow. The term $B$ is in essence an indication of the diameter and the number of that group of vessels relative to the amount of flow carried by those microvessels. Although $A$ has little meaning in terms of microvascular anatomy, it

**TABLE 2 Venules in Rabbit Omentum**

<table>
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<tr>
<th></th>
<th>Diam ($\mu$m)</th>
<th>$P_a$ (mm Hg)</th>
<th>$Q_{av}$</th>
<th>$P_a$ (mm Hg)</th>
<th>$P_d$ (mm Hg)</th>
<th>$R_aT$</th>
<th>$R_dT$</th>
<th>PA (mm Hg)</th>
<th>$R_{sar}$</th>
<th>$R_s$</th>
<th>$R_c$</th>
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$n = \text{number of measurements}; \text{other abbreviations are defined in the text.}$

* $10^{-3} \text{mm}^3/\text{sec.}$

† $\text{mm Hg}/10^{-3} \text{mm}^3/\text{sec.}$

![Figure 7](https://example.com/figure7.png)
does, however, indicate the relative size of a vessel in relationship to its flow.

Distribution plots of this kind can also be used to calculate pre- to postcapillary resistance ratios at various levels of the microcirculation. This was done by extrapolating the arterial and venular regression lines to the point where they intercept the capillary network (flows below 1 mm/sec) and designating these values as the pre- and postcapillary resistances. Thus, in the omental bed illustrated in Figure 7, the ratio of pre- to postcapillary R averaged between 3:1 and 3:5.

**MICROVASCULAR CHANGES FOLLOWING NOREPINEPHRINE**

The micro-occlusion method was found to be especially useful in the identification of the microvascular components involved in the response to selected stimuli. For this purpose an analysis was made of the response to systemic and to locally administered norepinephrine (NE) to illustrate the resolution of the technique.

When the drug was applied topically, it was possible to confine the response to the microcirculatory elements and to avoid changes in arterial pressure. In the accompanying graphs, the arteriolar and venular response to NE are shown. The upper two plots in Figure 8 depict the reaction to near-threshold concentrations and the two lower plots to near-maximal concentrations of the drug. The NE experiments were carried out in two stages. Pressure and flow in a selected arteriole or venule were recorded in the free-flowing state and after an upstream occlusion. The normal irrigation solution was then replaced by one containing NE, and after 30 seconds, when the maximum effect on local pressure and flow was present, the micro-

occlusion maneuver was repeated. The same procedure was then carried out a second time, only this time the vessel was obstructed downstream to the measuring site. It is for this reason that the steady state values of P and Q for a particular vessel were somewhat different for the two runs.

With a minimally effective dose of NE (4.0 μg/ml), pressure and flow in a 33-μm arteriole increase only slightly. The mediator produced a modest increase (+45%) in the resistance (R_u) of the precapillary extensions of the arteriole. The fact that the downstream reference pressure (P_d) fell by 4-5 mm Hg reflects the constriction of the precapillary vessels. Since the resistance (R_o) of the upstream vessels was increased (+55%), the larger feeding arterioles also responded to this dose of NE. A mirror image of this effect is seen when the response to the same dose of NE is studied by following the changes in the corresponding 40-μm venule. The close correspondence of the two sets of data is evident, R_u showing a 50% increase, except that in this protocol venous resistance R_d was only slightly affected.

The two lower plots in Figure 8 illustrate the response to NE (10 μg/ml) applied topically. In both vessels flow was drastically reduced (e.g., in the protocol on the left from 15 x 10^-3 mm^3 per sec to 4.5 x 10^-4 mm^3 per sec in a 44-μm arteriole). There is a substantial increase in the resistance of the smaller precapillary and capillary vessels as shown by the increase in R_u, a 3.3-fold change. However, R_w, which reflects the resistance of the feeding arteries, is increased about 6-fold. The fact that the upstream and downstream reference pressures (P_u and P_d at zero flow) remain unchanged indicates that the response to topical NE was confined to the segment of the microvascular bed being studied (vessels distributed between the upstream and downstream reference sites, P_u and P_d). The postcapillaries and collecting venules are relatively unresponsive to this dose of NE, as shown here for a 57-μm venule where R_d changes by only 20%.

In contrast, the effects of a slow intravenous infusion of NE are shown for two protocols in Figure 9. At this low concentration the mediator raises systemic blood pressure by 20-25 mm Hg, but has no demonstrable vasomotor effect on the portion of the microvascular network being studied. If one uses the conventional method of determining arterial resistance (arterial pressure minus micropressure divided by microvessel flow), arterial resistance will be assumed to have increased. With the micro-occlusion procedure it can be seen that although the slopes of the upstream and downstream dP/dQ regression lines for the network of vessels between the arteriole and venule remain essentially unchanged during the infusion, the upstream and downstream reference pressures (P_u and P_d) are shifted in proportion to the change in system blood pressure. It was concluded that with this concentration of NE, the predominant vasomotor change in this vascular segment occurred in the arterial vessels just proximal to the P_u reference point, while resistance in smaller vessels remained approximately unchanged.

Table 3 presents a more detailed analysis of pressure, flow, and resistance relationships following the three types of NE perturbations. In addition to the numerical values
for the various microvascular functions discussed above,
the protocols present the relative distribution of R values
among the three major segments of the peripheral circu-
lation—Rα (arteriolar), Rmc (microcirculatory), and Rv
(venular). The resistance of the arteriolar-precapillary
vessels accounts for 46% of the total resistance. The data
reveal the considerable range over which microvascular
resistance was changed.

Discussion

We have presented a method for studying the distribu-
tion of vascular resistance or impedance at the level of
the microcirculation proper. To the best of our knowledge
no comparable studies exist in the literature, primarily be-
because of the inability to measure pressure and flow simulta-
neously in the microvessels.

TABLE 3 Microvascular Resistance following Norepinephrine

<table>
<thead>
<tr>
<th></th>
<th>Diam (µm)</th>
<th>Pa (mm Hg)</th>
<th>Pq (mm Hg)</th>
<th>Rα*</th>
<th>Rmc*</th>
<th>PA (mm Hg)</th>
<th>Rmc</th>
<th>Rv</th>
<th>Rα</th>
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</thead>
<tbody>
<tr>
<td>Topical norepinephrine (4 µg/ml)</td>
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<tr>
<td>Arteriole (Fig. 8, top)</td>
<td>33</td>
<td>53.5</td>
<td>29</td>
<td>0.86</td>
<td>1.98</td>
<td>100</td>
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<td>C</td>
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<td>25.5</td>
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<td>0.39</td>
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<td>2.54</td>
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<td>99</td>
<td>0.24</td>
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<td>99</td>
<td>0.34</td>
<td>0.25</td>
<td>0.41</td>
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<td>(10 µg/ml)</td>
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<tr>
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<td>118</td>
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C = control; E = experimental; other abbreviations are defined in the text.
* mm Hg/10⁻³ mm³/sec.
In a branching system, instantaneous measurements at any given point cannot establish whether the resulting change in P vs. Q relations is due to an upstream or a downstream adjustment, or whether it is a combination of both. It is therefore necessary to test the system with some type of rapid transient; e.g., we have straddled the measuring site by an upstream and then by a downstream obstruction. The resulting transients can then be used to examine the resistance properties of the circuit. The functional characteristics of the network are defined in terms of five resistance values as shown in Figure 3: (1) \( R_u \), the resistances immediately upstream to a particular vessel; (2) \( R_m \), the resistances downstream of that vessel; (3) \( R_a \), the resistance between the major feeding artery and a location defined by the source pressure \( P_u \); (4) \( R_v \), the resistance between the reference pressure on the venous side \( P_v \) and the major venous vessel for the tissue; and (5) \( R_{mc} \), the microcirculatory segment intervening between this feeding artery and effluent vein. Thus, \( R_a + R_m + R_v \) represent the total resistance of the network.

The complex network is dealt with in a comparatively simple way by measuring two pressures and one flow. The P-Q plots under steady state conditions have characteristic slopes for arteries, arterioles, capillaries, venules, and veins which reflect the relative change in resistance encountered in the successive segments of the network.

The micro-occlusion procedure permits us to obtain data which describe how blood is supplied to a vascular segment as well as the resistance to flow in that segment and through it. This information thus describes how that segment acting alone can control flow. In those instances in which these vessels are capable of vasomotion, they will maintain control over that vascular segment as long it is operating independently of other segments—which presumably is the basic definition of local control.

For example, for a given 40- to 50-\( \mu \)m arteriole, the resistance \( R_a \) encountered downstream is 3–5 times larger than that in the arterial vessels upstream to the feeding arteriole. As a consequence, it would appear that the primary local determinant of the flow through the capillary vessels is the resistance in the more distal terminal arterioles and the precapillaries between this feeding arteriole and the capillary network proper. On the other hand, measurements made in vessels of near-capillary dimensions show that the upstream and downstream resistances are more nearly equivalent. Thus, at this given cross section of the vascular bed, the resistance of the contiguous upstream vessels leading into the capillary network represents the local factor that determines flow in any one of the capillary segments. In our equivalent network these two resistances are in series, and when a large resistance is in series with a small one it is the larger resistance that is the dominant factor in determining the flow at the site of measurement. This should not be construed as indicating that the upstream resistance in the arterial portion of the vascular bed has no effect on capillary flow. Inasmuch as the large arteriolar vessels supply as many as three to five different groups of capillaries, a change in upstream resistance will be distributed among all of these vessels at the same time.

The occlusion procedure defines this functional dichotomy in terms of a supplying pressure and a supply resistance for a particular microvascular segment. It is this functional characteristic that is the ultimate determinant of capillary pressure and volumetric flow rate. Under conditions in which two stimuli give rise to identical functional changes, the end result at the capillary level can be the same even though they might operate on different vessels. In this context, it should be noted that the small arteries and arterioles are believed to be under the control of the nervous system, whereas the smallest vessels (precapillaries and postcapillaries) almost entirely are influenced by local factors.

With the type of measurements made on an artery and a vein the vascular network has been divided into, at the minimum, five fairly well defined segments. We can then monitor how resistance changes in each segment. These resistances are the large arterial resistances, precapillary resistances, capillary segment resistance, postcapillary resistance, and large vein resistance. The boundaries are defined, starting from the artery and going to the vein, by the systemic pressure, the upstream occluded pressure, the occlusion site, the downstream occluded pressure, and the central venous pressures. These boundaries define four segments from the measurements made on the arteriole. Four more are defined by the venule occlusion and, at the maximum, only three of these segments are common, thus leaving five different segments defined with reasonably well defined boundaries. We purposely selected our vessel occlusion sites so that three of the venule segments were common to three of the arteriole segments. The limitation of the precision with which we can define the segment sites depends on the precision with which we can identify our boundaries and the number of different occlusion sites chosen.

The method can also be used to determine the effects of the geometry of the system on the distribution of pressure and flow. Since resistance data are provided on both sides of the microcirculatory network, calculations could be made of the relative resistances of different segments of the circulatory bed (\( R_u, R_m, R_v \)). The procedure gives average values for the network as a whole, which for purposes of comparison are frequently more meaningful than corresponding values based on single-vessel studies because of the considerable variability inherent in the latter measurements. It thus becomes possible to compare networks with different structural characteristics. A relatively complicated network is reduced to one that is easier to handle because only \( P \) upstream, \( P \) downstream, and flow at that point need to be identified. One of the disadvantages of the method is that it is difficult to characterize the resistance of individual structural components within a particular network. Since there is no unique way in which this simplified network can be expanded, it would be preferable, when such information is needed, to obtain detailed information regarding single vessels directly by using two micropipettes to measure the pressure drop along a selected vascular segment.

The micro-occlusion technique was found to be especially useful for identifying the vascular components that...
are affected by a particular stimulus, as illustrated with topically vs. systemically applied NE. The numerical values obtained for the resistance in the vessels of the mesentery and omentum by the microocclusion method cannot be readily compared with values in the literature for other tissues. However, the distribution of resistance values (i.e., arterial, capillary, venular) is essentially that which has been estimated by other approaches. Estimates of pre- to postcapillary resistance ratios (2.5:1 to 3.5:1) likewise approximate those in the literature for tissues such as skeletal muscle.

We have found that the reference pressures at zero flow are the same for the larger microscopic vessels in both the omentum and mesentery. This can be explained by the fact that in essence the microcirculation is a single input and output system despite differences in the structural organization of two networks. The microcirculation in the mesentery is made up of an anastomosing network with many parallel circuits, whereas in the omentum the bed consists of a progressively dichotomizing sequence with a single set of feeding and draining vessels. Close inspection of the omentum reveals a surprising amount of interconnection between the major feeding arterioles that supply separate capillary networks. In a comparable way, there are numerous interconnections between the larger venules (25–30 μm wide). As a consequence upstream and downstream resistances relative to the capillary network proper fall uniformly into the same range for both preparations.

A potential difficulty in our interpretation of the data stems from the fact that the occlusion data for any given transient are meaningful only when the geometry of the system does not change during the period of measurement. It was found that secondary adjustments to local disturbances in flow following microneedle occlusion of vessels require at least some 3–4 minutes. In the routine procedure that was adopted, the micro-obstructions lasted only some 15–20 seconds. The consistently linear nature of the resulting dP/dQ plots is strong proof for the passive nature of the response. Another question deals with the accuracy of the method. In measurements on larger microvessels, our ability to define the dP/dQ slope is limited by the small pressure drop along these vessels. In small vessels (30 μm and less) the AP becomes substantially larger and the slope of the regression line can be determined quite accurately. It is fortunate that under normal conditions microvascular hemostasis is achieved by adjustments of local blood flow in these smaller vessels.

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