LOCAL BLOOD FLOW IN HUMAN LEG MUSCLE MEASURED BY A TRANSIENT RESPONSE THERMOELECTRIC METHOD

WILLIAM PERL *and* SAMUEL A. CUCINELL
From New York University Research Service, Goldwater Memorial Hospital, Welfare Island, New York

ABSTRACT The initial transient response of a Gibbs type thermoelectric probe embedded in human resting leg muscle was used for absolute quantitative measurement of local blood flow per unit tissue volume (local perfusion). The probe consisted of two thermistor-containing needles, one of which was heated by a constant electrical power input. The temperatures of both thermistors were recorded continuously on a two-channel, fast-response recorder. Upon sudden occlusion of the blood flow to the leg, each temperature *vs.* time record exhibited a change of slope. The change in slope of the temperature difference, divided by the temperature difference, (degrees/minute degree) was identified with the local perfusion (milliliters/minute milliliter) existing just before occlusion. The local perfusions determined agreed in range and mean with literature values of average perfusion by venous occlusion plethysmography. The nature of the local blood flow measured by the present method is discussed relative to that by other methods.

INTRODUCTION

The thermoelectric probe introduced by Gibbs (1) has been widely used in various modifications as an indicator of local blood flow within a tissue [see review by Golenhofen and Hildebrandt (2)]. Despite attempts to use it quantitatively (3), this probe appears to have achieved *in vivo* only relative and approximate status, that is, the ability to determine approximate ratios of local blood flows (4–6). A suggestion has come from theoretical analysis as to how *in vivo* absolute status might be attained for this instrument (7 and 8). An initial test of this suggestion is reported herein.

Local blood flow is defined as the volume rate of blood flow ΔF leaving a small volume of tissue ΔV. Local perfusion is defined as the ratio $\phi = \Delta F/\Delta V$ (unit, ml/min.ml). The precision of these definitions will be increased subsequently. In the customary method of using the Gibbs probe, heat is injected at a constant rate into a small region of tissue. A "heat zone" around the injection site is thereby created, of order 1 cm^3 volume (2, 3, 7), within which the temperature is slightly

higher than in the surrounding tissue. The increase in temperature between a location outside and a location inside the heat zone, denoted the temperature increment, is measured continuously. If local blood flow goes up, so does the rate of removal of injected heat from the heat zone, and the temperature increment measured goes down. *Vice versa,* if local blood flow goes down, the temperature increment measured goes up.

The difficulties in quantitating the preceding method stem from the dependence of the temperature increment on other, more or less uncontrollable, variables besides local blood flow. Among these are: (*a*) *Heat conduction out of the heat zone;* which depends on thermal conductivity of the tissue and geometry of probe and tissue; (*b*) *Spatial variation of local blood flow in the heat zone;* for example, the blood flow in a large vessel traversing the heat zone affects the measured temperature increment in a complicated manner which depends strongly on degree of proximity of the blood vessel; (*c*) *Thermal time lag in the heat zone;* in response to a sudden (stepwise) change in local blood flow, the temperature increment does not change to a new steady value suddenly. Rather, the change is rapid at first, then increasingly slow, approximating the final steady value only after some time. For a heat zone radius of 5 mm this time is of order several minutes (see footnote 5). The temperature increment at a given time, therefore, does not bear a simple relationship to an irregularly varying blood flow at the same time.

The preceding variables are in principle eliminated in the present method. The method uses the initial transient response of the temperature increment of the heated probe to a sudden (stepwise) change in local blood flow (in contrast to the customary method which uses the final response, approximating the steady state). The method depends on the proposition that a stepwise change in local perfusion produces a simultaneous and proportional change in time rate of change of temperature increment; more precisely (see Appendix for derivation): if at some location and time, at which the local perfusion ϕ, the temperature increment u and its time derivative $\dot{u}$ have the values ϕ_1, u, $\dot{u}_1$, the local perfusion changes suddenly (discontinuously) to a value ϕ_2, then u remains momentarily unaltered but $\dot{u}$ changes suddenly (discontinuously) to a value $\dot{u}_2$ such that

$$\phi_1 - \phi_2 = K(\dot{u}_2 - \dot{u}_1)/u \tag{1}$$

where K is the ratio, $(\text{density} \times \text{specific heat})_{\text{tissue}}/(\text{density} \times \text{specific heat})_{\text{blood}}$.

Equation (1) expresses the principle of conservation of injected thermal energy under the condition of a sudden change in local blood flow. This change produces a sudden change in the rate of clearance of injected heat, represented by the left-hand side of equation (1) (after multiplying by $u \times (\text{density} \times \text{specific heat})_{\text{blood}}$). On physical grounds, temperature, hence temperature gradient, cannot change instantaneously. The same is therefore true for energy flow by heat conduction, which depends on temperature gradient. The only rate of energy change that can change

instantaneously in order to maintain energy conservation is that represented by the numerator of the right-hand side of equation (1) (for possible exceptions to this statement see Appendix). Since K is an independently known constant and u, $\dot{u}_1$, $\dot{u}_2$ are measured quantities, equation (1), if true, determines ϕ_1–ϕ_2 absolutely. In the present experiments, the blood flow to the region containing the temperature sensors was suddenly occluded. In this case $\phi_2 = 0$ and equation (1) determines the local perfusion ϕ_1 existing in the neighborhood of the temperature increment sensor just before occlusion.

The reason for the expectation that the preceding uncontrollable variables (*a*), (*b*), and (*c*) should be of small effect in the present method is that equation (1) expresses a relationship in a small (ideally infinitesimal) interval of space and time. The space interval involved is a tissue region around each temperature sensor only large enough to define a tissue temperature and a local perfusion. Such a region is of order several mm^3 volume (7). Variable (*b*) would then be of small effect if large blood vessels or other atypically perfused regions are more than about 1 mm distant from each temperature sensor, even though such vessels or regions may be in the heat zone. An experimental test to satisfy this criterion is given in the next section. The time interval involved in equation (1) extends from the time of blood flow change to a time sufficient to measure a change in slope of the temperature *vs.* time record. This interval, of order several seconds, is too short for heat conduction changes leading to thermal lag effects to develop appreciably. Variables (*a*) and (*c*) should then be of small effect. Thus, the basic reason to expect improvement in isolating the local blood flow variable by the present method as compared with the customary method is that the space-time interval of disturbance necessary to make the measurement is in effect shortened from the order cm^3 minutes to the order mm^3 seconds.

The following sections give the details of application of the present method to resting leg muscle of human subjects in normal health. This tissue is a fairly standard one for which the range of average perfusion has been well established by another absolute method, venous occlusion plethysmography. The literature values given by plethysmography form the basis for assessment of validity of the present method. A preliminary account has been given elsewhere, Cucinell and Perl (27).

METHODS

Experimental The probe comprised two temperature sensors and a heating element (Fig. 1). Each sensor was a thermistor resistance, enclosed in a No. 20 hypodermic needle at a distance of about 7 mm from the tip.[1] The heating element was a No. 36 (0.127 mm diameter) constantan wire about 17 cm long, of resistivity 0.40 ohms/cm, insulated with Teflon or polyurethane[2] (over-all diameter about 0.25 mm).

[1] Supplied by Tri-R Instruments, New York, New York.

[2] Supplied by Magnet Wire, Inc., New York, New York, and by Wilbur B. Driver Co., Newark, New Jersey.

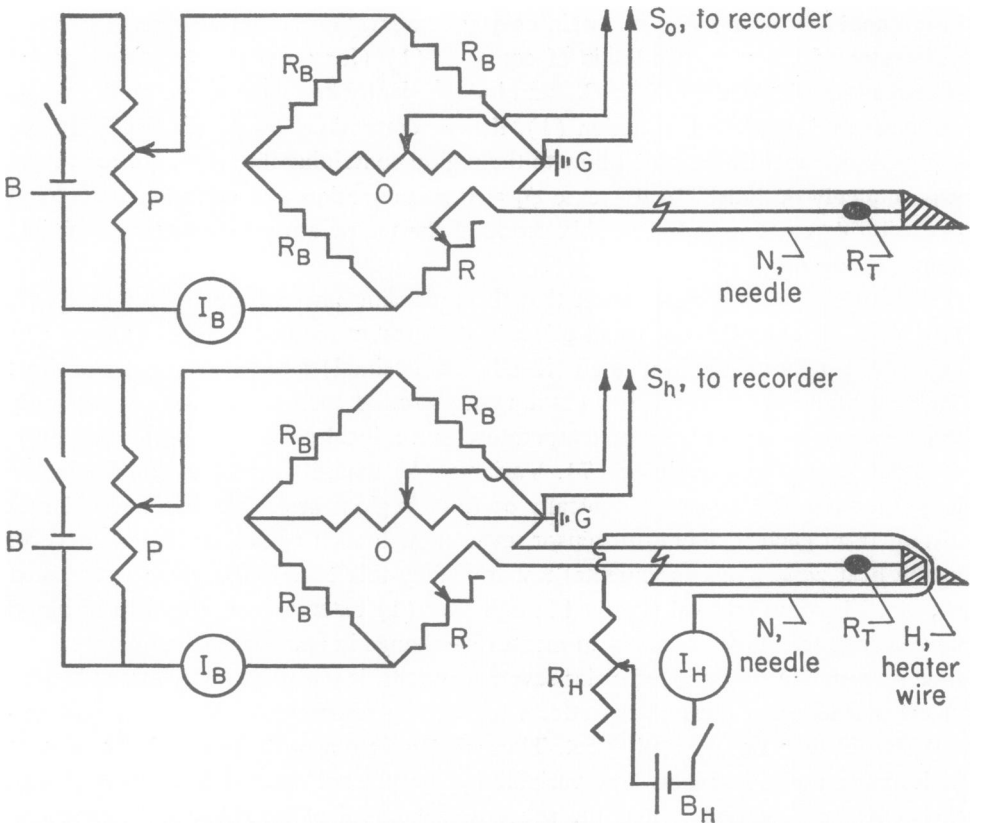

FIGURE 1 Diagram of apparatus. Resistance values: R_B, 2000 Ω; R, 10(1 + 10 + 100) Ω decade; P, 2000 Ω potentiometer; O, 2000 Ω, 10 turn Helipot; R_H, 50 Ω; R_T, 1500 Ω (35°C) glass coated thermistor. Power sources: B, 1.35 v mercury cell; B_H, 6 v storage battery. Meters: I_B, 0 to 1 ma; I_H, 0 to 0.5 a. G denotes ground. Outputs S_h, S_o to 2-channel, 0 to 1 mv, 1 second response time recorder. N, No. 20 steel hypodermic needle, 3.8 cm long. H, No. 36 constantan heater wire, Teflon or polyurethane insulated, connected to heavier copper wire at about 8.5 cm from tip of needle.

The wire ran along the outside of the needle, was looped through a hole in the bevel, and was connected to heavier copper wire at about 8.5 cm from the tip. Heating power was supplied by a 6 volt storage battery. Heating current was kept constant and in the range 0.1 to 0.3 amp. Each thermistor resistance was measured by a Wheatstone bridge circuit, of which the unbalanced output voltages were simultaneously recorded on a 2-channel, 1 mv, 1 sec., multispeed potentiometric recorder.[3] The bridge current of 0.4 ma was supplied by a 1.35 volt mercury cell. The thermistor was not heated noticeably by the 0.2 ma current through it. This current was kept almost constant as thermistor resistance varied, by varying the series decade resistance R in the opposite direction, to keep the

[3] Honeywell Brown Electronik Recorder.

TABLE I

LOCAL PERFUSION IN HUMAN GASTROCENEMIUS MUSCLE DETERMINED FROM INITIAL TRANSIENT RESPONSE TO OCCLUSION

Experiment	Subject	Age	Height	Weight	Occlusion	ϕ_1* ml/100 ml min.	
		yrs.	*cm*	*kg*		*range*	*mean*
1	A	28	180	91	9,*f*‡	0, 5.5	2.0
2	A	28	180	91	6,*f*	4.1,6.9	5.5
3	A	28	180	91	4,*f*	1.2,2.8	2.0
					5,*c*	1.4,2.6	1.9
4	B	44	190	83	9,*f*	0, 1.2	0.5
5	B	44	190	83	4,*f*	4.3,5.4	4.8
6	C	47	167	78	4,*f*	2.2,4.4	2.9
7	D	31	163	67	8,*f*	0, 1.4	0.4
					5,*c*	1.1,2.7	1.8
8§	E	29	193	87	6,*f*	2.4,9.7	6.6
9	F	27	175	69	11,*f*	2.5,6.5	4.4
Total					71	0, 9.7	2.9

* From equations (1) to (4), $K = 1$.

‡ Number denotes number of occlusions through first long occlusion, *f* denotes occlusion by manual pressure on femoral artery and vein, *c* denotes occlusion by inflation of cuff on thigh.

§ This experiment on left leg, all others on right leg.

unbalanced bridge voltage to less than 1 mv. The two thermistors were similar but not identical. The characteristic of each was about 1500 ohms and 48 ohms/°C at 35°C.

Nine experiments were performed on six male volunteers in normal health (Table I). In a typical experiment, the subject reclined in a wheel chair with both legs resting comfortably in horizontal position. The skin over the gastrocnemius muscle was washed with alcohol solution and anesthetized over an area of several square centimeters by cutaneous infiltration of procaine (about 1 ml of 2 per cent w/v procaine hydrochloride). Two punctures through the skin were made with a No. 18 needle which was then withdrawn. The probe needles had been previously sterilized chemically (soap and water scrubbing followed by 30 to 45 min. immersion in ioclide® solution GS 2). The probe needles were inserted one at a time through the skin punctures in distal-to-proximal direction, into the belly of the gastrocnemius muscle. In final position the two needles were approximately parallel to each other and about 1.5 cm apart. The unheated needle was advanced several millimeters farther than the heated needle so as to avoid the heat zone of the latter. The area of insertion was lightly covered with dry gauze.

After needle insertion, with heater power off, temperature recording was begun at low chart speed (1/3 inch/minute). A waiting period for stabilization of muscle temperature ensued, usually of about 30 minutes' duration. If pain, appreciable temperature inequalities between the needles, or temperature oscillations indicative of proximity to

large blood vessels were noted, one or both needles were moved.[4] Chart speed was next increased to 10 inches/minute so that temperature *vs.* time slopes could be conveniently measured (chart speed requirements can be estimated from equation (1) and the recorder *vs.* temperature calibration). A control occlusion of blood flow to the leg was then performed by one of two methods: (*a*) manual pressure on femoral artery and vein, applied in 1 to 2 seconds, or (*b*) inflation by hand bulb of a cuff around the thigh to a pressure of about 220 mm Hg. This inflation took about 8 seconds. Compressed air was used in some inflations, which reduced inflation time to 2 to 3 seconds. The occlusion was maintained for 15 to 40 seconds. If, during this interval, one temperature sensor showed a much higher change in slope than the other, the position of that needle was changed. This adjustment was not often necessary. The needle positions were acceptable when a control occlusion with heater off (no heat zone) produced moderate and similar changes in slope of both temperatures (see Discussion). Heating power was next applied, sufficient to produce a temperature increment of 2-4°C. In this process the temperature of the "unheated" needle sensor generally increased by 10 to 20 per cent of the temperature increment. Another waiting period of about 30 minutes ensued, for temperature stabilization of both needles. The blood flow to the leg was then occluded by method (*a*) or (*b*) for 15 to 40 seconds. After a series of such "short" occlusions, an occlusion of 4 to 5 minutes' duration was applied. Additional 15 to 40 second occlusions were subsequently performed. Heating power was then turned off. After a waiting period for temperature stabilization, several additional short occlusions were performed. The needles were then removed and examined for signs of blood or of tissue damage. Unheated muscle temperatures were in the range 34-37°C. Room temperatures were in the range 21-30°C and varied by about ± 1°C during an experiment. An experiment was of 4 to 5 hours' duration.

Calculational Thermistor resistance R_T (Fig. 1) is the fixed bridge arm resistance, 2000 ohms, minus the decade resistance R, plus the resistance equivalent of the unbalanced voltage as indicated by the recorder trace position S:

$$R_T = 2000 - R + S/A \tag{2}$$

The quantity A (chart divisions/ohm), determined experimentally as the ratio of recorder trace displacement to a change (10 ohms) in R, was a constant (the maximum unbalanced voltage, 1 mv, is a small fraction of the voltage, 400 mv, in a bridge arm).

Thermistor temperature θ is approximately linearly dependent on R_T in the present operating range (34-40°C). The constant A was fixed for each bridge, by adjusting the output potentiometers O, so that the change of S with sensor temperature θ was equal for the two sensors at their usual operating points. Sensor temperature θ could then be approximately replaced by equivalent chart distance $U = AR_T$ [also, the constant 2000 in equation (2) could be ignored, as only a ratio of temperature differences is involved in equation (1)]. The values of A were about 4.5 and 5.0 div/ohm for the two sensors respectively.

The temperature increment u in equation (1) was then determined as

$$u = (U_h' - U_0') - (U_h - U_0) \tag{3}$$

where U_h' is the equivalent chart distance for the sensor carrying the heater (subscript

[4] Pulse and respiratory frequencies indicate proximity to arteries and veins, respectively. The precautions followed were essentially those outlined in references (2), (4), and (9).

h), with heater power on (prime); U_o' is the equivalent chart distance for the sensor without heater (subscript o), with heater power on to the other sensor (prime); U_h, U_o are the corresponding control values with heater power off. The difference between $U_h - U_o$ at the beginning and end of each experiment averaged 5 per cent (range 2 to 8 per cent).

The difference $\dot{u}_2 - \dot{u}_1$ in equation (1) was determined as

$$\dot{u}_2 - \dot{u}_1 = (\Delta\dot{S}_h' - \Delta\dot{S}_0') - (\Delta\dot{S}_h - \Delta\dot{S}_0) \tag{4}$$

where $\Delta\dot{S}_h' = \dot{S}_{h2}' - \dot{S}_{h1}'$ is the graphically measured difference between the slope just after blood flow change (subscript 2) and just before blood flow change (subscript 1), of the recorder trace of the sensor carrying the heater (subscript h), with heater power on (prime); $\Delta\dot{S}_0'$ is similarly defined for the sensor without heater (subscript o); and the unprimed quantities are the corresponding control values for the same blood flow maneuver with heater power off. The control values averaged about 20 per cent (range 0 to 50 per cent) of the values with heater on.

The assumption of linear dependence of thermistor temperature on thermistor resistance was examined in several cases by calculating the temperature increments and time derivatives from the measured quantities, using the calibration curve of temperature *vs.* resistance for each thermistor (the values given in the legends of Figs. 2 and 3 were thus obtained). The results indicated that the assumption resulted in an approximately 10 per cent underestimation of the local perfusions. For present purposes this error is inconsequential. It may also be partially compensated by uncertainty of the value for K. The constant K in equation (1) was evaluated from the literature values: density of muscle and blood (10) = 1.06; specific heat of whole body tissue (11) = 0.83; specific heat of blood (12) = 0.87. The whole body tissue value of specific heat is more approximate than the other values. Assuming this value for muscle specific heat gives $K = 0.93$. The value $K = 1.0$ was used in the calculations. The error made thereby, if 0.93 is more nearly correct, tends to compensate the thermistor linearity error.

Correction of slope response because of instrument time lag was considered unnecessary, as rate of response of the probe to small step function changes in temperature was of order one hundred times the typical experimental response.

RESULTS

In nine experiments on six subjects, 109 occlusions were performed with heater on. Up through the first long occlusion (~ 4 min.), 71 occlusions yielded local perfusions in the range 0.5 to 9.7, mean 2.9, ml/min. 100 ml (Table I). The 38 occlusions after the first long occlusion yielded local perfusions in the range 1 to 28, mean 6.6, ml/min. 100 ml. In some experiments these post-long occlusion values systematically exceeded the pre-long occlusion values. Because of the possibility that in these cases the successive occlusions had produced a departure from resting muscle conditions, all 38 post-long occlusion values are omitted from subsequent consideration.

An original record (Fig. 2) of initial short control occlusion (heater off), occlusion (heater on), release after 5 minutes, and final short control occlusion (heater off) shows: the small and similar slope changes of both sensor temperatures in the initial and final control occlusions (Figs. 2*a* and *d*); the increase of slope, upon

occlusion, of the heater sensor temperature but not of the unheated sensor temperature (Fig. 2*b*); the new steady-state temperature increment (Fig. 2*c*); the large decrease of slope of the heated sensor temperature upon release from the 5 minute occlusion (Fig. 2*d*).

The local perfusion immediately *after* release from occlusion is given by equation (1) with $\phi_1 = 0$. For the short occlusions, held for 15 to 40 seconds, the slope changes immediately after release could be unambiguously measured in almost every case. Each perfusion thus determined was higher than the preceding preocclusion perfusion, ranging from 1.1 to 7.0, mean 2.5, times the preocclusion value. For the long occlusions, unambiguous slope determinations could be made in five experiments. These perfusions ranged from 2.8 to 16.0, mean 9.1, times the preceding preocclusion perfusions.

In one experiment the blood flow was occluded for 29 seconds and, in rapid succession, alternately released and occluded several times (Fig. 3). The perfusions just before occlusion or just after release, in ml/min. 100 ml, and the time intervals between the determinations were: 5(C_9), 29 seconds; (R_9) 22, 3 seconds; 20 (C_{10}), 6 seconds; (R_{10}) 28, 5 seconds; 21 (C_{11}), 11 seconds; (R_{11}) 15.

A possible effect of the rate of heat injection on the local perfusion being measured was looked for in several experiments. The heater power input was varied to give temperature increments between 1° and 4°C. At each power level several short occlusions were performed. No systematic effect on calculated local perfusion was noted, indicating that the injected heat was acting as a true tracer in this range of temperature increment. The upper temperature increment was chosen as 4°C because of the finding, Hensel *et al.* (4), in resting human gastrocnemius muscle, that above this value heating power begins to deviate from proportionality to temperature increment, indicating an effect of temperature increment on local blood flow.

The limit of sensitivity of the present instrument was about 0.5 ml/min. 100 ml. This value was determined from the approximate minimum slope detectable, about 4 chart div/min., at a temperature increment of 4°C (about 800 chart divisions).

In one experiment a small degree of bleeding was encountered upon insertion of a needle. In all other experiments the needles, after withdrawal, appeared quite clean.

DISCUSSION

The preceding values of local perfusion may be compared with literature values of average perfusion obtained by venous occlusion plethysmography. Cooper *et al.* (13) found for the resting forearm musculature the range of values 1.8 to 9.6, mean 3.9 ml/min. 100 ml. Plethysmographic studies on the leg (14, 15) yield values (average of skin and muscle) within this range. The range and mean values by the present initial transient method (Table I) are in good agreement with the plethysmographic results.

The increase of blood flow immediately following an interval of total occlusion,

denoted reactive hyperemia, has likewise been measured by venous occlusion plethysmography. Abramson *et al.* (16) found after 2.5, 5 and 10 minutes of occlusion of the forearm increases of average perfusion to some 5.5, 6.0 and 6.5 times the preocclusion resting values, respectively. Thus, the longer the occlusion, the higher was the blood flow immediately after release. Increases of this order have been found in numerous other plethysmographic studies (17-21). The increases obtained by the initial transient method, after 15 to 40 seconds of occlusion (range 1 to 7.0, mean 2.5) and after 4 to 5 minutes of occlusion (range 3 to 16, mean 9) are compatible with the plethysmographic results.

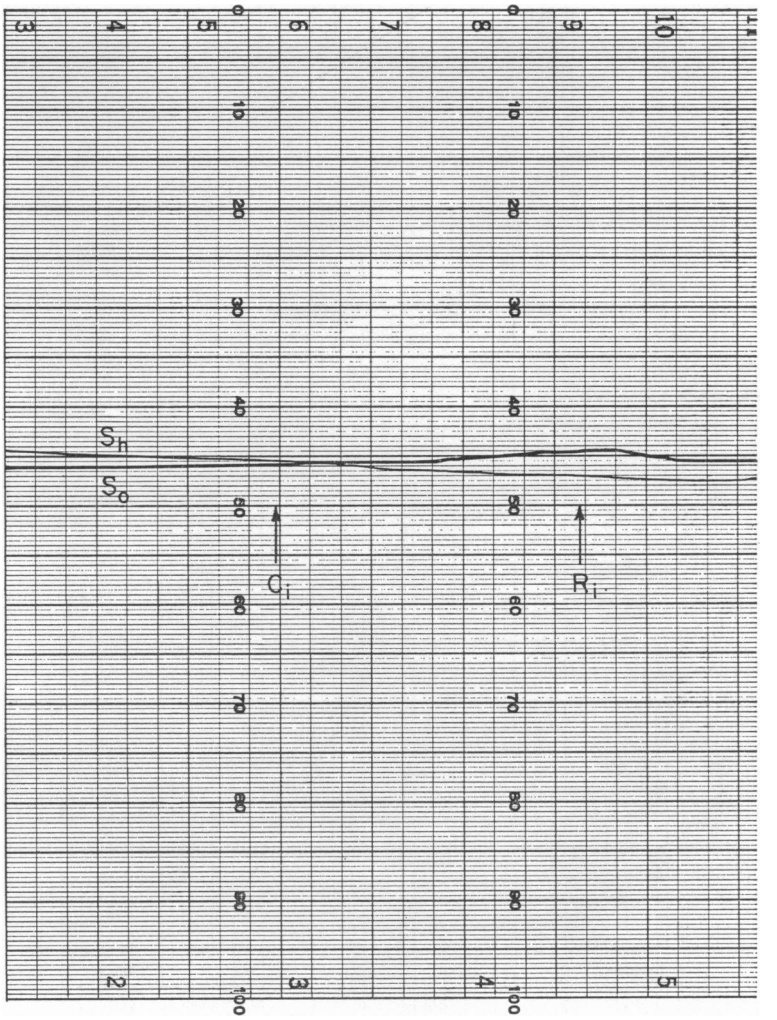

FIGURE 2*a*

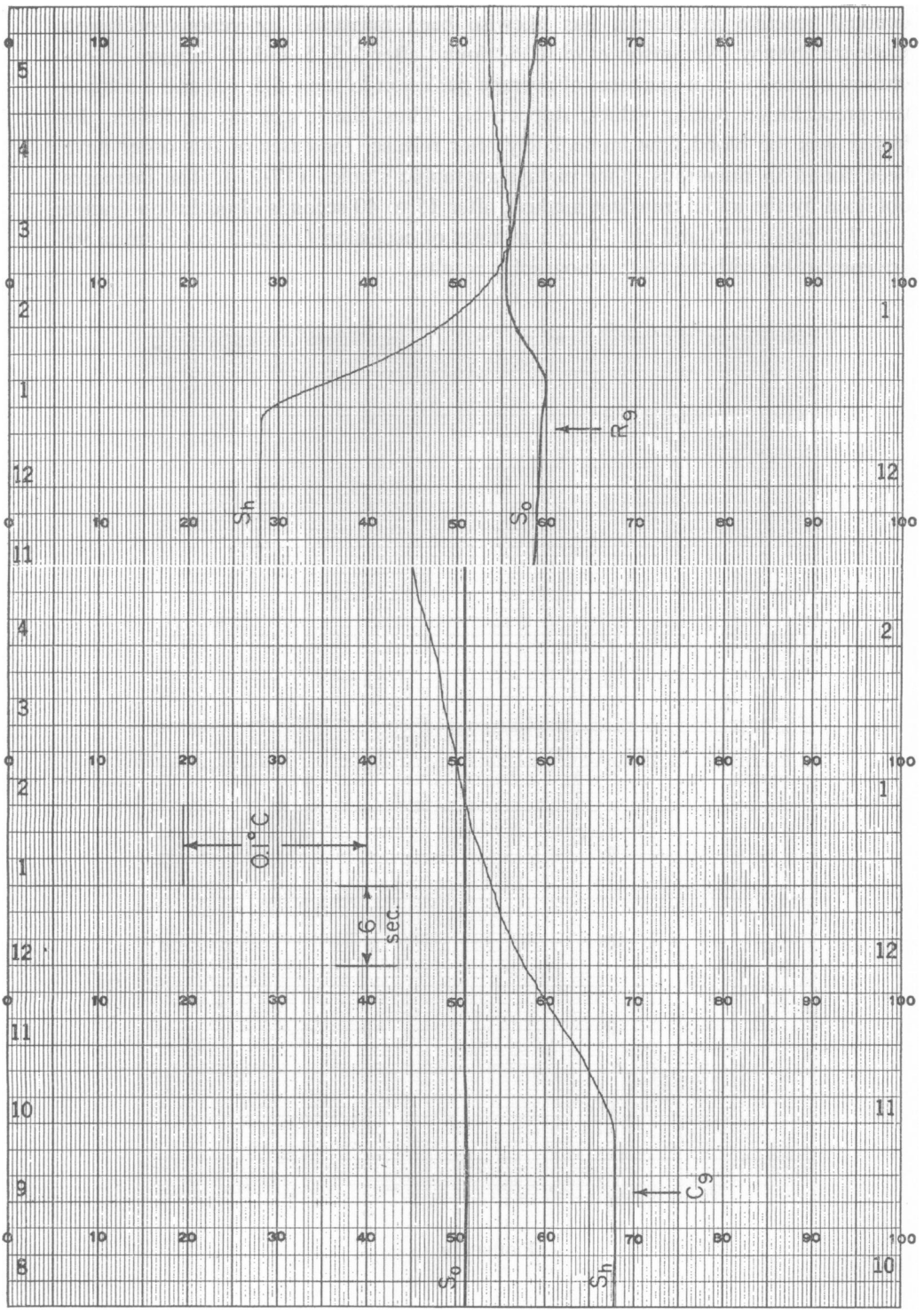

FIGURE 2b and c

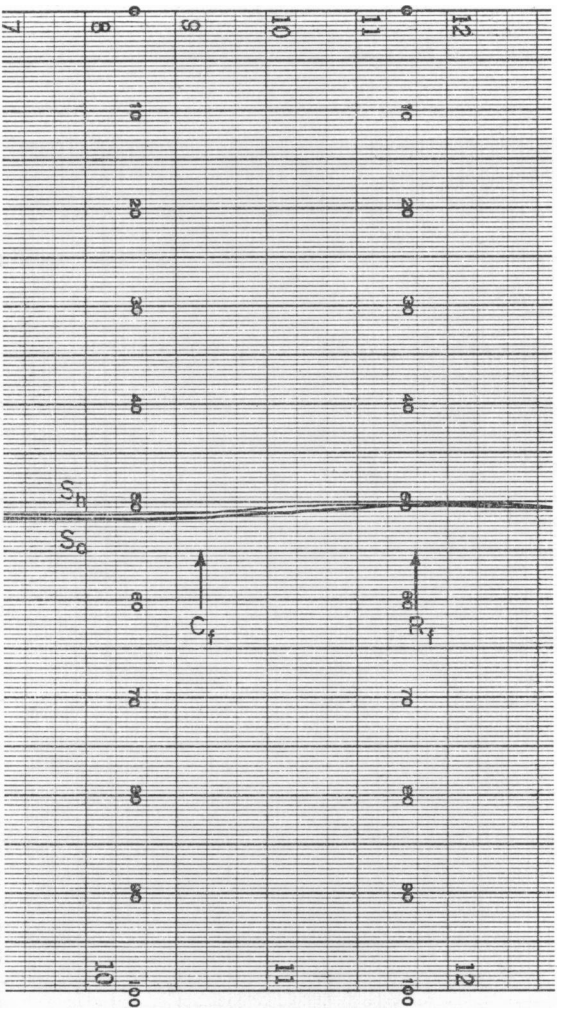

FIGURE 2*d*

FIGURE 2 Original record of occlusion and release maneuvers, Experiment 8. Probe needles in left gastrocnemius muscle. Occlusions by femoral pressure method.
(*a*) Heater off, control occlusion C_t at time 7:11 p.m., $\theta_h = 35.5°C$, $\theta_o = 35.7°C$. Occlusion maintained for 20 seconds. Release at R_t.
(*b*) Heater on, occlusion C_9 at time 9:03 p.m., $\theta_h' = 39.4°C$, $\theta_o' = 37.1°C$, $u = 2.5°C$, $\dot{u}_2 - \dot{u}_1 = 0.225°C/minute$, $\phi_1 = 9.0$ ml/minute 100 ml.
(*c*) Heater on, release R_9 at time 9:08 p.m., $\theta_h' = 39.6°C$, $\theta_o' = 37.0°C$, $u = 2.8°C$, $\dot{u}_2 - \dot{u}_1 = -1.51°C/minute$, $\phi_2 = 54$ ml/minute 100 ml, $54/9.0 = 6.0$.
(*d*) Heater off, control occlusion C_f at time 10:25 p.m., $\theta_h = 36.6°C$, $\theta_o = 36.8°C$, Occlusion maintained for 14 second. Release at R_f.
Notation: *S*, recorder trace; θ, temperature of sensor; *u*, temperature increment; Dot, time derivative; prime, heater on; Subscripts: *h* (carrying heater), *o* (without heater), 1 (before blood flow change), 2 (after blood flow change).

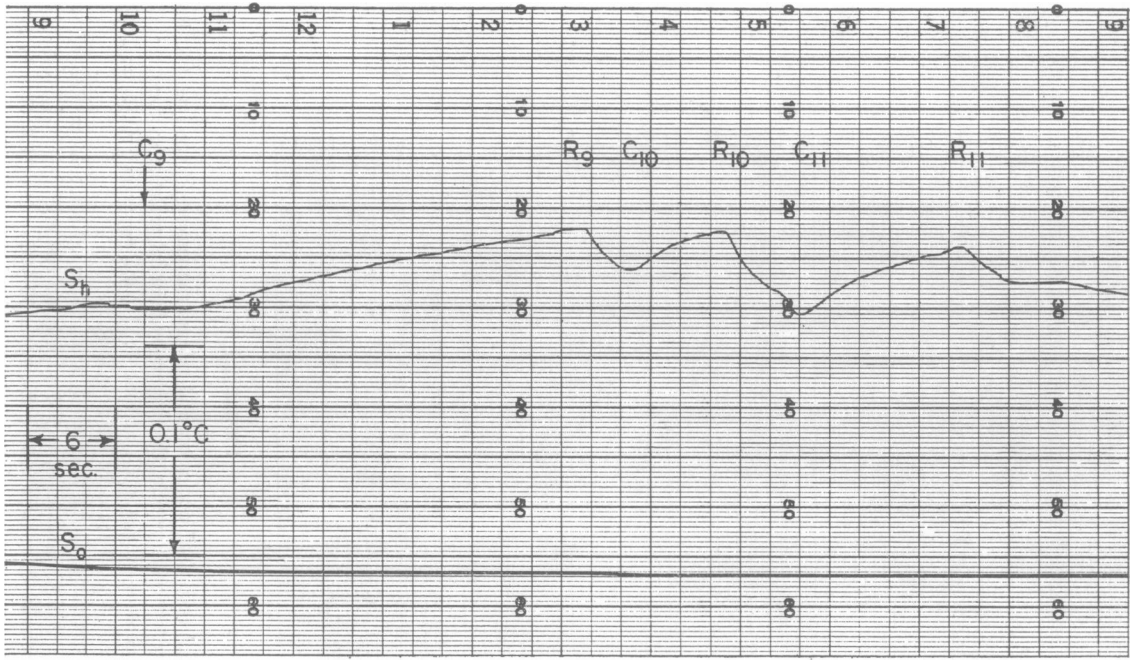

FIGURE 3 Original record of alternating occlusion (C_n) and release (R_n) maneuver, Experiment 5. Pribe needles in right gastrocnemius muscle. Occlusions by femoral pressure method. At C_9 $\theta_h' = 38.4°C$, $\theta_o' = 35.5°C$, $u = 33.0°C$, $\dot{u}_2 - \dot{u}_1 = 0.16°C$/minute, $\phi_1 = 5.3$ ml/minute 100 ml.
Notation as in Fig. 2.

An internal check of the present method is provided by the alternating occlusion and release maneuver (Fig. 3). The values of local perfusion 22 ml/min. 100 ml after release R_9, 20 before occlusion C_{10}, 28 after release R_{10}, 21 before occlusion C_{11}, are consistent with development and partial recovery from reactive hyperemia. The somewhat low final value, 15 after release R_{11}, might have been due to imperfect maintenance of femoral pressure or to opening up of collateral circulation (the time interval between occlusion C_{11} and release R_{11} was greater than the previous time intervals). This maneuver tests the ability of equation (1) to yield a value of local perfusion where the initial state is far from steady, both in time as regards local perfusion and in space and time as regards heat zone temperature distribution.

Also observed were some differences from the predictions of the idealized theory. After occlusion by application of femoral pressure, delays of several seconds often occurred before the temperature slope changed (Fig. 2*b*). Some possible causes are: (*a*) insulation and metal thickness surrounding the thermistor may give about 1 second delay (special case of (*c*) below); (*b*) local blood flow may continue for a time after occlusion of the blood flow at a proximally distant location. The blood might flow into local venous reservoirs or around local circuits; (*c*) the heated temperature sensor may be in a region of undetectably low perfusion at a distance d from another region of higher perfusion, both regions being in the heat zone. Upon occlusion, the time rate of temperature rise in the higher perfused region would propagate as a "heat signal" to the temperature sensor. Propagation times $t = 1, 4, 10$ seconds yield approximate propagation distances $d = 0.3, 0.6$ and 1 mm, respectively.[5] These distances are well within the heat zone dimension of about 5 mm radius (2, 3, 7). Time delay due to "heat front" propagation should be accompanied by a gradual rather than sudden development of sensor temperature change and a tendency toward such behavior was observed (Fig. 2*b* and *c*). Shorter observed time lags than in Fig. 2*b* were associated with more clean-cut slope change.

Another observed difference from ideal behavior was that, upon occlusion and before the expected development of the heating response, an initial transient cooling of the heated temperature sensor took place. Upon release of occlusion the reverse occurred, heating before the expected cooling. This behavior was associated only, though not always, with the cuff method of occlusion, never with the femoral pressure method. This presumably artifactual initial behavior might have been caused by a slight shift of the heated needle, upon cuff occlusion, into a cooler part of the

[5] The well-known approximate relation for diffusion or heat conduction (22) $s^2 \sim \chi t$ with the thermal diffusivity $\chi \sim 10^{-3}$ cm^2/sec. (9) yields the cited values. Note also that the thermal diffusivity is about 100 times greater than the diffusion constant of small molecules in watery tissue (23). In a given time, therefore, a "heat wave front" would penetrate to about 10 times the distance as a "molecular diffusion wave front."

heat zone with reverse shift upon cuff release (2). Whenever it occurred the method of occlusion was changed from cuff to femoral pressure.

In two experiments the cuff method of occlusion was free of the preceding artifact and could then be compared with the femoral pressure method (Table I). In Experiment 7 on subject D, the cuff method gave somewhat higher perfusions (1.1 to 2.7) than did the femoral pressure method (0 to 1.4). In Experiment 3 on subject A, however, both methods gave almost the same range of perfusions (1.3 to 2.7). These results indicate that the femoral pressure method of occlusion did not produce a systematic understimation of perfusion. Such understimation might occur, for example, if the occlusion were incomplete or collateral circulation existed.

Subject A was tested on two other occasions, Experiments 1 and 2, by the femoral method. The ranges of perfusion obtained (0 to 5.5) and (4.1 to 6.9) respectively included and were higher than the range by both methods in Experiment 3 (1.3 to 2.7). Subject B, tested on two occasions by the femoral method, yielded a low range in Experiment 4 (0 to 1.2) and a higher range in Experiment 5 (4.3 to 5.4). These results indicate that the range of variability of the "resting" muscle condition in the present experiments is about the same for one individual as from one individual to another.

The theoretically predicted type of initial transient response to occlusion and release of peripheral blood flow is evident in much previous work (2, 4). In this work the recorder chart speeds were too slow to permit quantitative evaluation of slope changes. However, the order of magnitude of the slope responses appears to be similar to that encountered herein.

The present experiments imply that the initial transient method measures the capillary blood flow through a small volume of tissue, divided by this volume, the volume being several mm^3 neighboring on the heated temperature sensor. The evidence for this conclusion is, first, that the similarity of slope response of both temperature sensors under the same conditions; *i.e.*, occlusion with heater off, implies that both sensors are in a capillary region (see Appendix for argument). Second, the development of a temperature *vs.* time slope change within 5 seconds after occlusion implies that this "heat signal" could not have propagated from more than about 1 mm away from the heated temperature sensor.[5] Third, is the comparison with venous occlusion plethysmography. This method yields a rate of change of limb volume which is identified with the rate of arterial inflow to the limb. The rate of arterial inflow, divided by the limb volume [the limb muscle in the case of Cooper *et al.* (13)], may be regarded as an average value of the range of capillary blood flow per unit volume existing throughout the limb. This identification stems from the basically parallel, or mammillary, flow connection of the individual capillary beds to the large vessels. The order of magnitude agreement between plethysmography and the present method implies, therefore, that the local blood flow measured by the present method is, to the same order, a capillary blood flow; that is, local

heat clearance by large vessel blood flow is not predominantly involved in the present method of measurement.

Graf and Rosell (5) have shown that the customary, quasi steady-state response of a Gibbs type probe[6] in cat hind leg muscle correlated well with total blood flow from the muscle, only when the local heat clearance was predominantly by large vessel blood flow. They showed that their probe placements were of two types: (*a*) The probe was near (within about 1 mm) one or more large (about 1 mm diameter) blood vessels. A change in total blood flow produced a fast (seconds) response of temperature increment. The maximum change in temperature increment correlated well with the change in total blood flow; (*b*) The probe was distant 5 mm or more from the nearest large blood vessel. With this placement the temperature increment responded slowly (minutes) and with poor correlation of the maximum change in temperature increment with change in total blood flow.

The present conclusion, that by the initial transient method the Gibbs type probe measures a local capillary blood flow, does not conflict with Graf and Rosell's conclusions if the probe placements in the present experiments are identified with their poor response placements. The results then indicate that the two different heat clearance methods of using the same type of probe are not measuring the same quantity. The quasi steady-state method measures in relative terms a local blood flow through large vessels in close proximity to the probe. The initial transient method measures in absolute terms a capillary blood flow per unit tissue volume, likewise in close proximity to the probe.

A question arises as to the nature of the "capillary" that is being measured by the initial transient method. Presumably arterioles and venules contribute to heat clearance, along with the various types of anatomical capillaries. Thus, a "heat exchange capillary" is not necessarily similar, or similarly permeable to, a "sodium exchange capillary" (24, 25). The simultaneous determination and comparison at one tissue site of the clearance rates of several substances including thermal energy might help to answer this question.

The order of magnitude agreement of the present results with plethysmographic values demonstrates at least a similar degree of validity of equation (1). A more precise estimate of validity requires a more closely applicable comparison method. The initial transient method of measurement is possible *in vivo* in any body tissue accessible to a hypodermic needle and amenable to a temporary (several seconds) blood flow occlusion and should form a useful complement to the quasi steady-state method of Gibbs.

---

[6] The probe was of Hensel's design (4). Two thermocouples 1 cm apart and a heater wire were embedded in a steel tube or a plastic rod of 1 mm diameter. The heated thermocouple junction was near the tip. The cat hind leg was skinned and total venous outflow was measured by a drop counter in the femoral vein.

APPENDIX

Theory

The starting point is the partial differential equation expressing conservation of energy[7] (7, 8)

$$K\partial\theta/\partial t = \text{div } (\chi_b \text{ grad } \theta) + \phi(\theta_a - \theta) + \gamma_b \tag{5}$$

where

$$K = \frac{\rho c_p}{\rho_b c_{pb}}, \qquad \chi_b = \frac{\kappa}{\rho_b c_{pb}}, \qquad \gamma_b = \frac{h}{\rho_b c_{pb}} \tag{6}$$

div, grad are the usual vector expressions for spatial derivatives, θ is the local tissue temperature, θ_a is blood temperature at entry to the local tissue volume element, κ is the thermal conductivity of the tissue at zero blood flow (cal/cm sec. °C); ρ is the density (gm/cm^3) and c_p the specific heat (cal/gm °C) of the tissue; ρ_b is the density and c_{pb} the specific heat of blood; ϕ is the local perfusion, or capillary blood flow per unit tissue volume (ml/ml sec. = sec.$^{-1}$); h is the local rate of thermal energy production per unit tissue volume (cal/sec. cm^3). Of the preceding quantities, density and specific heat are considered constant, whereas the others may vary with location (x, y, z) and time t.

Equation (5) states that the time rate of change of temperature in a small volume element of tissue, ($\sim$1 mm^3), which contains statistically many ($\sim 10^4$) capillaries, randomly distributed and oriented (isotropic case) is the sum of contributions from: (*a*) Heat conduction (Fourier's law). (*b*) Thermal energy clearance by local blood flow [Fick's principle plus the perfusion-limited assumption that local venous blood temperature equals local tissue temperature[5] (7)]. (*c*) Thermal energy production minus consumption, due to internal sources (chemical reactions) and external sources (heating power to probe). The effect of larger blood vessels which are too few in number to be regarded statistically is included implicitly in the present formulation as a boundary condition, to be satisfied in integrating equation (5) throughout space (the heat zone) and time. Such inclusion would be necessary, for example, in deriving the steady-state response of the probe, if large vessels are within the heat zone. In the present application only a local solution of equation (5) is desired, namely, temperature change in an infinitesimal region of the heat zone, for an infinitesimal time before and after a sudden (discontinuous) change in local blood flow. For this purpose boundary or initial conditions are in principle irrelevant.

Consider first a single unheated temperature sensor embedded in the tissue of interest. Let the blood flow to the tissue be suddenly changed, corresponding ideally to a discontinuous change of ϕ. On physical grounds the temperatures θ and θ_a, hence also the spatial gradient of θ, cannot change discontinuously in time. Assume for the moment that thermal conductivity κ and heat source parameter h likewise do not change discontinuously when ϕ does. To accommodate the change in ϕ, therefore, the only remaining possibility of change in equation (5) lies in $\partial\theta/\partial t$. Subtracting equation (5) just before occlusion (subscript 1) from equation (5) just after occlusion (subscript 2) and denoting partial time derivatives by dots yields

$$(\phi_1 - \phi_2)(\theta - \theta_a) = K(\dot{\theta}_2 - \dot{\theta}_1) \tag{7}$$

The occlusion maneuver yields experimental values for θ and $\dot{\theta}_2 - \dot{\theta}_1$. There are, however, two unknowns, $(\phi_1 - \phi_2)$ and θ_a, in equation (7) (even if θ_a were known, equation (7) would

[7] The steady-state version of this equation has been used by Wissler (26) in calculating temperature distributions in the body.

not yield $\phi_1 - \phi_2$ accurately because θ_e does not differ greatly from θ). A second relation between θ_e and $\phi_1 - \phi_2$ is obtained by switching on the heater power. A new and slightly elevated temperature distribution $\theta'(x, y, z, t)$ is thereby created, satisfying the equation

$$K\partial\theta'/\partial t = \text{div } (\chi_b \text{ grad } \theta') + \phi(\theta_e - \theta') + \gamma_b' \tag{8}$$

where $\gamma_b' - \gamma_b$ represents the heat source distribution of the heating element, and χ_b, ϕ, θ_e are assumed unaffected by the higher temperature (tracer assumption for injected heat, discussed later). Repeating the preceding change in blood flow and subtraction procedure on equation (8) yields

$$(\phi_1 - \phi_2)(\theta' - \theta_e) = K(\dot{\theta}_2' - \dot{\theta}_1') \tag{9}$$

Subtracting equation (7) from equation (9) eliminates θ_e, and yields an expression for $\phi_1 - \phi_2$ in terms of measured quantities,

$$(\phi_1 - \phi_2)u = K(\dot{u}_2 - \dot{u}_1) \tag{10}$$

where $u = \theta' - \theta$ is the temperature increment. Equation (10) corresponds to use of a single temperature sensor, alternately heated and unheated. The main assumptions are:

1. The injected heat may alter the local blood flow being measured. This may be checked either within the method itself, by decreasing the heater power, as measured by $\theta' - \theta$, and noting any systematic change in $\phi_1 - \phi_2$, or by comparison with an independent method.
2. The injected heat may alter the local entering blood temperature θ_e. If the capillaries are taken as the anatomical or "molecule-exchange" capillaries, then θ_e would in general increase to some value θ_e' when tissue temperature θ is elevated to θ'. The result is that a falsely low value of $\phi_1 - \phi_2$ is obtained from equation (10). If the dependence of $\theta_e' - \theta_e$ on $\theta' - \theta$ is other than linear, this effect can in principle be evaluated by varying the heater power, that is, $\theta' - \theta$. If the dependence is linear, comparison with an independent method appears necessary. This effect should be small in those capillary beds where the capillaries develop abruptly from the arteries, with few intermediate branchings.
3. The local entering inflow temperature θ_e may change for internal body reasons between the times of measurement with heat source off and heat source on. This effect can be corrected for by using a second temperature sensor, placed essentially outside of the heat zone. Denote this sensor by subscript o and the sensor near the heat source by subscript h. The occlusion maneuver with heat source off now yields, instead of equation (7),

$$(\phi_1 - \phi_2)(\theta_h - \theta_{eh}) = K\Delta\dot{\theta}_h \tag{11}$$

$$(\phi_1 - \phi_2)(\theta_0 - \theta_{e0}) = K\Delta\dot{\theta}_0 \tag{12}$$

and with heat source on (denoted by prime), instead of equation (9)

$$(\phi_1 - \phi_2)(\theta_h' - \theta_{eh}') = K\Delta\dot{\theta}_h' \tag{13}$$

$$(\phi_1 - \phi_2)(\theta_0' - \theta_{e0}') = K\Delta\dot{\theta}_0' \tag{14}$$

where $\Delta\dot{\theta}_h = \dot{\theta}_{h2} - \dot{\theta}_{h1}$, etc. The subtraction procedure, equations [(13) — (14)] — [(11) — (12)], and the assumption that the change in arterial temperature at sensor h between the times of heater off and heater on, $\theta_{eh}' - \theta_{eh}$, equals that at sensor o, $\theta_{e0}' - \theta_{e0}$, yields

$$(\phi_1 - \phi_2)[(\theta_h' - \theta_0') - (\theta_h - \theta_0)] = K[(\Delta\dot{\theta}_h' - \Delta\dot{\theta}_0') - (\Delta\dot{\theta}_h - \Delta\dot{\theta}_0)] \tag{15}$$

Equation (15) was used to evaluate the present data [see equations (3) and (4)].

4. The use of a second sensor also guards against the possibility that the first sensor is in an "abnormally" perfused region such as near a large blood vessel. Thus suppose the local perfusion is ϕ_h at sensor h and ϕ_o at sensor o and blood flow is occluded with heater off. Then equations (11) and (12) become

$$\phi_h(\theta_h - \theta_{eh}) = K\Delta\dot{\theta}_h \tag{16}$$

$$\phi_0(\theta_0 - \theta_{e0}) = K\Delta\dot{\theta}_0 \tag{17}$$

The sensors are supposed so placed that (*a*) their temperatures are the same, or $\theta_h = \theta_o \equiv \theta$, and (*b*) their slope response to blood flow occlusion is the same, or $\Delta\dot{\theta}_h = \Delta\dot{\theta}_o$. The ratio of equations (16) and (17) then gives

$$\frac{\phi_h}{\phi_0} = \frac{\theta_{e0} - \theta}{\theta_{eh} - \theta} \tag{18}$$

The most plausible solution of equation (18) would seem to be equality of local perfusions $\phi_h = \phi_o$ and equality of local arterial inflow temperatures $\theta_{eh} = \theta_{eo}$ [if ϕ_h were much greater than ϕ_o one would expect that the linear velocity of blood flow would be higher at h than at o. Hence there would be less time for the blood to equilibrate with the local tissue and $\theta_{eh} - \theta$ would be greater than $\theta_{eo} - \theta$. This condition would contradict equation (18)]. Equality of local perfusions makes it unlikely that either sensor could be near a large blood vessel, since both sensors would then have to be very similarly situated geometrically with respect to this vessel. The conclusion is, that sensors placed to satisfy conditions (*a*) and (*b*) above are most likely situated in capillary regions of equal local perfusion.

5. The thermal conductivity κ of the tissue might possibly change discontinuously upon sudden occlusion or other discontinuous change in blood flow. For example, local circular paths of blood flow might suddenly develop in the capillaries upon total occlusion. Although the average flow from arterial to venous side is zero, such local flows would promote heat interchange. Hence the macroscopic effect would be an increase in κ, as compared, for example, with κ for dead tissue at zero perfusion. Suppose total occlusion produces a discontinuity $\Delta\chi_b$ in thermal diffusivity and a discontinuity Δ grad χ_b in its spatial gradient. Then in the transition from equation (5) to equation (7) the additional terms $\Delta\chi_b$ div grad θ + (Δ grad χ_b) · grad θ appear. If both the first and second spatial derivatives of θ vanish at the location of the temperature sensors, both terms disappear. This is the case if the tissue temperature is reasonably uniform with heater power off and if sensor h with heater power on is at a sufficiently "flat-topped" center of symmetry of the heat zone temperature increment. These conditions are approximately met with the present probe arrangement. The converse theoretical suggestion may be noted, that information as to possible temporal discontinuity in thermal conductivity upon blood flow change may be obtainable by locating a sensor asymmetrically with respect to the heater element.

6. The local blood flow (not the heat zone temperature distribution) is isotropic, that is, either the capillaries are short relative to the heat zone dimensions ("point" heat sinks) or there is no preferred orientation of the capillaries (capillary jungle). In the non-isotropic case the partial differential equation (5) must be altered and the concept of local perfusion as capillary blood flow per unit volume becomes incomplete in characterizing local capillary blood flow (see Appendix A of reference 7).

We thank Drs. Eugene Y. Berger, Wei Chen, Robert L. Hirsch, Hildegard R. Maricq, J. Murray Steele, and Mr. Harry Wolfson for timely assistance and discussion, and Mrs. Leonora LaForte for help with the manuscript.

This work was supported in part by the United States Public Health Service under Grants HE-07482-02 and HD-00672-08 and in part by the Health Research Council of the City of New York under Contract U-1089.

Received for publication, March 5, 1964.

REFERENCES

1. GIBBS, F. A., A thermoelectric blood flow recorder in the form of a needle, *Proc. Soc. Exp. Biol. and Med.*, 1933, **31**, 141.
2. GOLENHOFEN, K., and HILDEBRANDT, G., Das Verfahren der Wärmeleitmessung und seine Bedeutung für die Physiologie des menschlichen Muskelkreislaufes, *Arch. Kreislauf-forsch.*, 1962, **38**, 23.
3. GRAYSON, J., Internal calorimetry in the determination of thermal conductivity and blood flow, *J. Physiol.*, 1952, **118**, 54.
4. HENSEL, H., and RUEF, J., Fortlaufende Registrierung der Muskeldurchblutung am Menschen mit einer Calorimetersonde, *Arch. ges. Physiol.*, 1954, **259**, 267.
5. GRAF, K., and ROSELL, S., Untersuchungen zur fortlaufenden Durchblutungsregistrierung mit Wärmeleitsonden, *Acta Physiol. Scand.*, 1958, **42**, 51.
6. DOSEKUN, F. O., GRAYSON, J., and MENDEL, D., The measurement of metabolic and vascular responses in liver and muscle with observations on their responses to insulin and glucose, *J. Physiol.*, 1960, **150**, 581.
7. PERL, W., Heat and matter distribution in body tissues and the determination of tissue blood flow by local clearance methods, *J. Theoret. Biol.*, 1962, **2**, 201.
8. PERL, W., An extension of the diffusion equation to include clearance by capillary blood flow, *Ann. New York Acad. Sc.*, 1963, **108**, 92.
9. HENSEL, H., and BOCK, K. D., Durchblutung und Wärmeleitfahigkeit des menschlichen Muskels, *Arch. ges. Physiol.*, 1955, **260**, 361.
10. SPECTOR, W. S., Handbook of Biological Data, Philadelphia, W. B. Saunders Co., 1956, pp. 51, 295.
11. BURTON, A. C., and EDHOLM, O. G., Man in a Cold Environment, London, Edward Arnold and Co., 1955, 41.
12. EPSTEIN, W., VISSCHER, M. B., STISH, R., and BALLIN, H., Specific heat of canine blood, *J. Appl. Physiol.*, 1963, **18**, 843.
13. COOPER, K. E., EDHOLM, O. G., and MOTTRAM, R. F., The blood flow in skin and muscle of the human forearm, *J. Physiol.*, 1955, **128**, 258.
14. BARCROFT, H., and SWAN, H. J. C., Sympathetic Control of Human Blood Vessels, London, Edward Arnold and Co., 1953, 15.
15. SHEPHERD, J. T., Physiology of the Circulation in Human Limbs in Health and Disease, Philadelphia, W. B. Saunders and Co., 1963.
16. ABRAMSON, D. I., TUCK, S., JR., YVONNE BELL, MITCHELL, R. E., and ZAYAS, A. M., Effect of short periods of arterial occlusion on blood flow and oxygen uptake, *J. Appl. Physiol.*, 1961, **16**, 851.
17. BARCROFT, H., HENSEL, H., and KITCHIN, A. H., Comparison of plethysmograph and thermo-electric needle records of calf blood flow during intravenous adrenaline infusions, *J. Physiol.*, 1955, **127**, 7P.
18. DORNHORST, A. C., and WHELAN, R. F., The blood flow in muscle following exercise and circulatory arrest: the influence of reduction in effective local blood pressure, of arterial hypoxia and of adrenaline, *Clin. Sc.*, 1953, **12**, 33.
19. MURPHY, R. A., JR., MCCLURE, J. N., JR., COOPER, F. W., JR., and CROWLEY, L. G., The effect of Priscoline, papaverine and nicotinic acid on blood flow in the lower extremity of man. A comparative study, *Surgery*, 1950, **27**, 655.
20. LANDOWNE, M., and KATZ, L. N., A critique of the plethysmographic method of measuring blood flow in the extremities of man, *Am. Heart J.*, 1942, **23**, 644.

21. EICHNA, L. W., and WILKINS, R. W., Blood flow to the forearm and calf. II. Reactive hyperemia: factors influencing the blood flow during the vasodilatation following ischemia, *Bull. Johns Hopkins Hosp.*, 1941, **68,** 425.
22. CRANK, J., The Mathematics of Diffusion, Oxford, Clarendon Press, 1956, 36.
23. HÖBER, R., Physical Chemistry of Cells and Tissues, Philadelphia, The Blakiston Company, 1945, 13.
24. BRUNER, H. D., *Methods Med. Research,* 1960, **8,** sect. III, 222.
25. KETY, S. S., Measurement of regional circulation by the local clearance of radioactive sodium, *Am. Heart J.*, 1949, **38,** 321.
26. WISSLER, E. H., Steady-state temperature distribution in man, *J. Appl. Physiol.*, 1961, **16,** 734.
27. CUCINELL, S. A., and PERL, W., Estimation of blood flow in human muscle by a thermoelectric technique, *The Pharmacologist,* Fall, 1963, **5,** 233.