Comparison of Various Vascular Beds in Man
Their Responses to a Simple Vasodilator Stimulus

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Blood flow to the extremities and kidneys was measured simultaneously in normal subjects, hypertensive patients and patients with obliterate arterial disease of the lower extremities. The latter group showed diminished basal flow in the lower extremities, increased basal flow in the upper extremities, and a delayed and diminished response to reflex heating, compared with the normal and hypertensive subjects. In all three groups, the increase in extremity blood flow was regularly accompanied by a concomitant decrease in renal blood flow. No significant change in arterial pressure was observed.

Attempts to correlate rate of regional blood flow with clinical manifestations of arterial disease have so far not been too successful for several reasons. The methods employable in man are limited and, by necessity, indirect; base line data have been difficult to obtain, and knowledge of the interplay between various vascular beds is fragmentary. It was believed, therefore, that simultaneous measurements of blood flow to the skin and muscle of an extremity and of a viscerai organ such as the kidney might give promise of a better understanding of shifts of blood flow under physiologic and pharmacologic stimuli. The present study concerns the response of kidney and extremity to the simple vasodilator stimulus devised by Gibbon and Landis.

Methods

Of the many methods available for estimating blood flow to the extremities of man, plethysmography was chosen as the most accurate and most direct in spite of its known difficulties. A rather complete description of the apparatus is deemed necessary since the principles involved have only been used heretofore on very small objects such as finger tips or toe tips.

1. Blood Flow to the Extremities

An air transmission plethysmograph has been developed, using a strain gauge to measure volume changes in terms of very small pressure changes (3 or 4 mm. Hg), too small to affect blood flow. Readable pulse curves from parts as large as foot plus leg have been obtained with this instrument. The stopcock arrangement on the operation board (fig. 1) provides for prompt connection from plethysmograph to strain-gauge, plethysmograph to air, strain-gauge to recorder and strain-gauge to air. There are also connecting stopcocks for sudden venous occlusion, using a large reservoir in which the air is kept at the desired pressure (30 mm. Hg for foot, hand, or hand and forearm; 40 mm. Hg for foot and leg). The apparatus has two channels permitting simultaneous recording of plethysmographic changes from two limbs if desired. The direction from which the impulse enters the strain-gauge determines the direction of the slope; one of the channels produces a rising, the other one a falling slope on the graph. Calibration of the pressure changes in terms of volume is made by injecting 5 ml. of air before each single set of three recordings of blood flow. The instrument proved to be quite sensitive and the return to the baseline after release of occlusion is exact. The sensitivity of the recording device permits use of a large dead space, making it possible to keep conditions within the chamber quite constant, as evidenced by continuous temperature.
Fig. 1. View of controls of operation board of strain gauge plethysmograph.

Fig. 2. Plethysmographic chamber with thermocouples in place. A = occlusion cuff; B = metal flange; C = rubber cuff; D = plastic chamber; E = thermocouples to toe and leg; F = connecting part with strain gauge; G = connection of cuff with reservoir.

Fig. 3. Sample of tracing representing the change of volume of the extremity after venous occlusion. On this channel to the strain gauge, the descending slope indicates increase in volume of limb. Note the exact return to baseline after release of occlusion.

Formula: \[ \frac{600 \times L}{K \times V} = \text{Blood flow (ml. per minute per 100 ml. of tissue)} \]

600 \times 3.2 \times 500 = 7.68 \text{ ml. per 100 cc. of tissue per minute}

\[ K = 0.5 \text{ cm. per cubic centimeter}; \quad V = 500 \text{ cc.} \]

\[ L = 3.2 \text{ cm.} \]

In turn, the large size of the dead space requires great constancy of environmental conditions as afforded by the constant temperature room.

For sealing the limb within the plastic case, greased foam rubber covered with sheet rubber and a rubber cuff for direct contact with the skin is used. Leaks in the apparatus are easily detected by injecting a small amount of air (5 ml.) and waiting for 30 seconds to see whether the displaced baseline remains horizontal.

Good seals have been obtained without evident obstruction of the veins, and responses to venous occlusion have been prompt. After sudden venous occlusion proximal to the plethysmograph, the linear portion of the rising slope of the curve is used to calculate the rate of blood flow (fig. 3).

The volume of the part of the limb enclosed in the chamber is calculated from the effect which known volumes placed within the chamber have on the deflection caused by the addition of 5 ml. of air. The larger the volume of the limb, the smaller the remaining volume in the chamber and the greater the deflection. From the time scale a distance equivalent to 10 seconds is measured on the baseline and a perpendicular (L) erected at this point. Blood flow in ml. per minute in 100 ml. of tissue is calculated from the formula:

\[ \frac{600 \times L}{K \times V} \]

wherein L is the perpendicular rise in slope in centimeters during 10 seconds, K is the calibration constant of the recording apparatus in millimeters deflection per milliliter of change in volume, and V is the volume of the enclosed limb segment in milliliters. Changes in blood flow through the arm and hand or leg and foot taken together and then through the hand or foot alone are used to calculate
by difference the rate of flow through forearms and legs.

When measuring the blood flow through an extremity one actually is dealing with three vascular beds rather than with one: the skin, the deeper soft tissues, mostly muscle, and the bones. No attempt was made to estimate the blood flow to the bones.

To obtain evidence as to what portion of total blood flow went to muscle and what portion to skin, estimation of the ratio of skin to muscle in the arms and legs and in the hands and feet was attempted.* Anteroposterior and lateral soft tissue x-ray films of the extremities of nine people of different build and sex were made and from measurements of the areas of skin and of muscle, estimates of the relative volume of skin and muscle were made. The approximations for skin-muscle ratios varied in leg and forearm from 0.23 to 0.55, averaging 0.36 for the leg, 0.31 for the forearm, and in hand and foot from 3.0 to 5.0, averaging 4.1 for the hand and 4.0 for the foot. These ratios indicate that plethysmographic records of hands and feet represent predominantly blood flow through the skin, while those of the forearms and legs represent predominantly blood flow through the deeper tissues (except bone), that is, mainly muscle.

2. Renal Blood Flow

Changes in renal plasma flow were measured by the technic of maintaining a constant infusion of sodium para-aminohippurate. Arterial blood samples were taken from an indwelling 21-gauge Courand needle inserted into a brachial artery. Three samples were taken at 15-minute intervals to establish a baseline, and three more at the height of vasodilatation in the extremities as indicated by surface temperature and plethysmographic readings. For simplicity the assumption was made that the rate of infusion of the substance was the same as the rate of excretion in the urine, an assumption justified by the work of Berger, Farber and Earle. In following this assumption the clearance calculation can be stated as $C = IV/P$ where $C$ is the clearance of para-aminohippurate in milliliters per minute and corresponds to the renal plasma flow. $I$ is the concentration of para-aminohippurate in the infusion in milligrams per milliliter, $V$ is the rate of infusion in milliliters per minute and $P$ is the plasma concentration of para-aminohippurate in milligrams per milliliter. Para-aminohippurate in a trichloracetic acid filtrate was deacetylated by heating for one hour in a tenth normal hydrochloric acid solution. The solution was then diazotized and coupled, using the Marshall-Bratton procedure. Renal blood flow was calculated from plasma flow on the basis of concurrently determined hematocrits.

* We wish to thank Dr. Louis Bergman, Associate Professor of Anatomy at New York University College of Medicine, for his friendly advice.

### Procedures

The principle upon which we have relied in testing vasomotor responses is that vasodilator agents and procedures should be tested against a mild vasoconstrictor stimulus and vice versa. The baseline data for testing vasodilator responses have all been obtained in an environment of 20 C. and 50 to 55 per cent humidity, conditions which afford a mild vasoconstrictor stimulus. After adaptation to the environment has been ascertained to have taken place (surface temperature being recorded quasi-continually on a six-channel Speedomax), heating of the body is induced by the Gibbon-Landis procedure by heating an extremity in a water bath at 44 to 45 C., maintained for 45 minutes in normal reactors. In cases of marked obliterator arteriosclerosis where a delayed reaction is encountered, the procedure is extended until skin temperature has leveled off but never for longer than 90 minutes; there may be an extremely rare case in whom no reaction can be elicited.

This type of experiment, measuring blood flow to the extremities and to the kidneys simultaneously, has been performed on 11 normal subjects, 6 patients with sustained essential hypertension, and 10 patients with obliterative arterial disease of the lower extremities.

### Results

As is well known, heating the body produces reflex vasodilatation in the nonimmersed extremities. Essentially, this effect was regularly observed in all three types of patients studied. The average changes observed in the three groups are given in table 1.

Simultaneous decrease in renal blood flow occurred with the increase in flow to the extremities. The maximal decrease in renal blood flow varied from 10 per cent to 13 per cent and coincided roughly in time with the

| Table 1.—Influence of a Standard Vasodilator Stimulus (Landis-Gibbon Test) on the Blood Flow of the Extremities under Basal Conditions after Adaptation to an Environment of 20 C. |
|-----------------|-------|-------|-------|-------|
|                 | Foot  | Leg and Foot | Hand | Forearm and Hand |
| Normals         | 1.1   | 8.6      | 1.1   | 3.1     | 1.6     | 19.0       | 1.7     | 7.4      |
| Arteriosclerotic diseases | 0.3   | 3.6      | 1.8   | 2.8     | 2.5     | 15.1       | 1.1     | 7.0      |
| Hypertensives   | 0.6   | 11.8     | 1.3   | 4.3     | 1.2     | 13.2       | 0.6     | 5.1      |

Figures represent averages expressed in cc. of blood per 100 cc. of tissue per minute.
maximal increase in blood flow to the extremities (fig. 4).

Arterial pressure was measured throughout the experiment. In no instance was there any significant change in either systolic or diastolic pressure.

**DISCUSSION**

Several points of interest emerge from these studies. One was that patients with obliterative arteriosclerosis had in general lower basal flows to the feet and higher ones to the hands than had the normals and the hypertensive patients. These findings might be interpreted as an indication that the hands compensate for the inability of the feet to meet demands for elimination of heat. Such an interpretation finds support in the fact that skin temperature curves show that in contrast to normals the hands of patients with obliterative arteriosclerosis in the lower extremities take over in part the task of coarse adjustment to the environment.

Our findings corroborate those of Page\(^\text{23}\) who showed that renal flow decreased when the body was heated by diathermy. The work of Radigan and Robinson\(^\text{23}\) who produced evidence that renal blood flow in a hot environment was considerably lower than in a cool environment and that exercise regularly lowered blood flow through the kidney, is also of interest in this connection. Barklay and co-workers\(^\text{24}\) and Chapman and associates\(^\text{25}\) showed likewise that heavy exercise reduced renal blood flow considerably. It seems clear, therefore, that whenever blood flow to areas of the extremities where glomi are abundant increases appreciably in order to meet a demand for increased heat dissipation, renal blood flow decreases. The inverse response of different vascular beds to a simple vasodilator procedure suggests that vasodilator drugs might well be studied with regard to regional effects on the vascular tree.

The shift in blood flow from visceral (renal) to peripheral (extremity) vascular channels took place in the absence of any significant change in arterial pressure.

**SUMMARY**

1. No significant difference was found between normal persons and hypertensive patients in either their basal extremity flow or in their response to reflex heating. People with obliteratorive arterial disease of the lower extremities show diminished basal flow in the diseased parts compensated by increased basal flow in the upper extremities, and their response to reflex heating is delayed and diminished.

2. In a cool environment increase in blood flow to the lower extremities in all three groups occasioned by reflex heating (Gibbon-Landis test)\(^\text{29}\) was regularly accompanied by a decrease in renal blood flow of from 10 per cent to 13 per cent.

3. No significant change in arterial pressure was observed during the experiments.

**SUMARIO ESPAÑOL**

La circulación de las extremidades y los riñones fué medida simultáneamente en sujetos normales, pacientes hipertensos y pacientes con enfermedad oclusiva arterial de las extremidades inferiores. El último grupo mostró una circulación basal en las extremidades inferiores disminuida, aumentada en las extremidades superiores, y una respuesta retardada v disminuida al reflejo térmico, com-
parado con los sujetos normales e hipertensos. En los tres grupos el incremento en circulación de la extremidad fué regularmente acompañado por un decremento concomitante en circulación renal. No se observó cambio significativo alguno en presión arterial.

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