The Mechanism of Limb Segment Reactive Hyperemia in Man

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The roles of vasodilator metabolites and/or reduced local intra-arteriolar pressure in producing the reactive hyperemia which follows the sudden release of arterial occlusion were studied. It was found that slight increases of metabolic activity during the period of occlusion increased the reactive hyperemia considerably. Maintenance of intra-arteriolar pressure during arterial occlusion depressed the resultant reactive hyperemia. It was concluded that both factors contribute to the reactive hyperemia. The blood flow “debt” incurred during arterial occlusion was almost invariably “overpaid” during the reactive hyperemia period.

In 1872 Cohnheim described flushing of the skin following release of arterial occlusion. This phenomenon, reactive hyperemia, was later shown to be due to generalized vasodilatation with a resultant increased volume flow of blood to the previously ischemic extremity. Explanations of this vasodilatation tend to fall into two general groups. One holds that reactive hyperemia is produced by vasodilator metabolites, while the other attributes reactive hyperemia to the arterial pressure reduction which follows sudden arterial occlusion. This paper describes observations designed to determine the relationship of these two factors to the vasodilatation of reactive hyperemia in man. In addition, data were obtained on the relationship between the total reactive hyperemia blood flow and the calculated blood flow “debt” incurred during arterial occlusion.

Methods and Results

Each group of experiments will be described separately as to purpose, method and results.

General. All subjects were young (20 to 27 years), healthy, normotensive, muscular males. They were studied in the recumbent position with the posterior portion of the test forearm at heart level (10 cm. anterior to the back). Room temperature ranged from 25 to 29 C. in different experiments and remained relatively constant (±1 C.) during any one experiment. Subjects were unclothed except for undershirt and shorts, but were given enough covering to maintain comfort. Every attempt was made to keep subjects comfortable. They were encouraged to relax both mentally and physically, but were not allowed to sleep. They were asked not to talk except to notify the experimenter of any unpleasant stimuli. They remained in the supine position for at least 30 minutes before experiments were begun.

In all experiments a pneumatic cuff 8 cm. wide was placed around the wrist and inflated to 200 mm. Hg prior to each plethysmographic procedure.

Plethysmographic Procedure. The forearm was placed in a rigid, water-filled, variable depth plethysmograph. The water level within the plethysmograph was such that the hydrostatic pressure approximated venous pressure. Thus the effective venous pressure was low and the vein walls were freely distensible at the start of each blood flow determination. Forearm volume changes were recorded on a moving kymograph by a Brodie bellows and those that occurred during venous occlusion at the elbow (10 cm. wide pneumatic cuff) were measured as blood flow in cc. per minute. Various venous occlusion pressures were utilized at the onset of each experiment and the minimum occlusion pressure required to produce the maximum rate of venous filling was selected for use. This pressure was usually about 20 mm. Hg. Venous occlusion was applied suddenly in all cases.

Arterial occlusion of desired duration was produced by inflating a 10 cm. wide pneumatic cuff around the upper arm to 250 mm. Hg pressure. The pressure in this cuff was applied and released suddenly. The forearm remained motionless during the occlusion unless stated otherwise. The volume of the limb segment within the plethysmograph was determined by subtracting the capacity of the plethysmograph with the limb in place from the previously determined total plethysmograph capacity. Blood flow was calculated as cc./minute/100 cc. of limb. Plethysmographic water temperature was maintained at 32 C. in all experiments. Air pressure above
the water in the plethysmograph (necessary to keep
the Brodie bellows open) was one to two mm. of
water unless stated otherwise.

Following arterial occlusion periods of 5, 10 or
15 minutes, blood flows of 5 seconds duration were
determined at 15-second intervals until they re-
turned nearly to normal, when flows were taken at
30-second intervals until blood flow was constant.
Blood flow measurements were started at the instant
of release of arterial occlusion, unless stated other-
wise, by inflating the venous occlusion cuff just prior
to release of arterial occlusion.

The reactive hyperemia blood flow (referred to as
RHBF hereafter) was determined in the following
manner: Each blood flow determination was plotted
against time. The area subtended by the resultant
curve in excess of resting blood flow (see below) was
obtained planimetrically. This figure was converted
to cc. per 100 cc. of limb by simple calculation.

A single figure for resting blood flow for an entire
experiment was used. Three to five blood flow de-
terminations were carried out before each arterial
occlusion and they were averaged. These figures
(four to six in number usually) were in turn averaged
and this final figure was the average resting blood
flow in cc. per minute per 100 cc. of limb.

The calculated blood flow "debt," or the amount
of blood which would have passed through 100 cc.
of limb at rest during a period equal to the time of
circulatory arrest, was obtained as follows: The
resting blood flow in cc. per 100 cc. of limb per min-
ute was multiplied by the duration in minutes of
arterial occlusion used to produce the reactive
hyperemia.

RHBF and calculated blood flow "debt." The
RHBF was compared with the calculated blood flow
"debt" following periods of arterial oc-
cclusion of 5, 10 and 15 minutes. Forty-three
tests were done on six subjects in 16 experi-
ments. The percentage excess of blood flow
above the predicted "debt" became greater as
occlusion was prolonged. The relationship be-
between RHBF and calculated blood flow "debt"
is illustrated in figure 1. The average value for
several RHBF's following a given duration of
arterial occlusion in any one experiment was
plotted. All points which fall above the 45
degree line represent RHBF's in excess of calcu-
lated blood flow "debt." All of the forty-three
RHBF's except two exceeded the calculated blood flow "debt." These two tests occurred in the
same experiment on three of the subjects. These
data are also plotted in figure 1 in that lines
connect those determinations done on the
same subject. The results of these determina-
tions agreed with those in the random studies
above in showing that all of the individual
RHBF's exceeded the calculated blood flow
"debt."

Vasodilator Metabolites. The effect of increas-
ing the local metabolic activity of the muscles
was tested. Metabolic activity was increased by
having the subject perform mild exercise for a
short period during occlusion so that locally
elaborated vasodilator metabolites would be
trapped in the forearm. The subject squeezed
a rubber cylinder 4 cm. in diameter as firmly as
possible 36 times during a 30-second period.

![Graph showing relationship between RHBF and calculated blood flow "debt" incurred during arterial occlusion. For discussion see text.](http://circres.ahajournals.org/DownloadedFrom)
This exercise was not of sufficient intensity to produce pain or other unpleasant stimuli in the subject's arm, or to cause any alteration in systemic blood pressure or pulse rate. It was done in such a way as to utilize all of the muscles of the forearm. A 30-second period of exercise was carried out either as soon as arterial occlusion was applied, at the beginning of the second minute of occlusion, or during the last 30 seconds of occlusion. The RHBF following 30 seconds of exercise during a 30-second period of occlusion was also determined. The RHBF following a period of 5 minutes of arterial occlusion alone was measured in the same experiment. Finally, the effect upon RHBF of the maximum possible amount of ischemic exercise was measured by having the subject squeeze the cylinder to the point of complete local exhaustion.

The RHBF's following 5 minutes of arterial occlusion and a 30-second period of exercise performed in the order given above were 62.8 cc., 58.2 cc. and 57.2 cc. respectively. In the same experiment the RHBF following 30 seconds of exercise and only 30 seconds of arterial occlusion (35.8 cc.) added numerically to the RHBF resulting from five minutes of arterial occlusion alone (22.0 cc.) equaled 57.8 cc. (fig. 2).

The RHBF which followed five minutes of arterial occlusion with exercise to the point of local exhaustion was 277.0 cc. The exercise was started at the beginning of the second minute of occlusion and required 1.25 minutes before such exhaustion occurred. It produced extreme pain in the arm as well as the unpleasant false sensation of arm motion. These symptoms lasted until the release of arterial occlusion.

Intravascular Pressure. The effect on RHBF of intra-arterial pressure fall following sudden occlusion of the circulation was next evaluated. Arterial pressure was maintained at a high level by preventing arterial blood volume "run-off" into the venous system. The arm was first

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**Fig. 2.** Left panel, graph showing effects on RHBF of 30 seconds exercise performed at various intervals during five minutes arterial occlusion.

Right panel, graph showing the RHBF in same subject following five minutes arterial occlusion alone and during 30 seconds exercise with arterial occlusion during exercise only.

Ordinates, blood flow cc./min./100 cc. arm. Abscissae, time in min.
congested with the arterial occluding cuff at 70 mm Hg for three minutes, then congestion was continued at 95 mm Hg for an additional two minutes and finally arterial occluding pressure of 250 mm Hg was added to the same cuff for a period of 10 minutes. Previous experience had shown that ample time was allowed for venous pressure to reach levels equaling those of the cuff. The RHBF was measured at the conclusion of the circulatory arrest. In all of these experiments it was necessary to wait for a period of 7 seconds after release of circulatory arrest before accurate blood flow measurements could be made, due to the initial venous distension. The resultant RHBF (fig. 3 and table 1) was 21 to 51 per cent less than that obtained without prior congestion.

To rule out any possible effect of an increased volume of blood per se in the extremity, the effective intravascular pressure was reduced to zero by external counterpressure sufficient to exceed the intravascular pressure as follows: The same experiment as above was repeated except that immediately after the application of arterial occlusion just proximal to the plethysmograph, pressure within the plethysmograph was raised to 100 mm Hg rather than 1 or 2 mm Hg during the 10-minute period of arterial occlusion. This procedure resulted in a RHBF whose mean value was not significantly different from that produced by 10 minutes of arterial occlusion alone (fig. 3). Venous congestion alone for five minutes produced no measurable RHBF.

The combined effects of intravascular pressure and vasodilator metabolites were tested in the following experiment: The forearm was congested for five minutes, then arterial occlusion was applied for one minute. During this occlusion 30 seconds of exercise was carried out as described above. Circulatory arrest was

**TABLE 1.—Effect of Prior Venous Congestion on Reactive Hyperemia Blood Flow Following 10 Minutes Arterial Occlusion.**

<table>
<thead>
<tr>
<th>Subject Number</th>
<th>Reactive Hyperemia Blood Flow without Prior Venous Congestion</th>
<th>Reactive Hyperemia Blood Flow with Prior Venous Congestion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27.2</td>
<td>17.4</td>
</tr>
<tr>
<td>1</td>
<td>30.4</td>
<td>17.7</td>
</tr>
<tr>
<td>2</td>
<td>42.6</td>
<td>21.0</td>
</tr>
<tr>
<td>2</td>
<td>45.0</td>
<td>28.4</td>
</tr>
<tr>
<td>2</td>
<td>37.0</td>
<td>22.2</td>
</tr>
<tr>
<td>3</td>
<td>36.8</td>
<td>25.1</td>
</tr>
<tr>
<td>Mean</td>
<td>36.5</td>
<td>23.1</td>
</tr>
</tbody>
</table>
released and RHBF was determined. The experiment was then repeated without prior congestion. In the first experiment the RHBF (following 30 seconds exercise during one minute arterial occlusion in a congested arm) was 60.5 cc; whereas the same exercise performed without the maintenance of arterial pressure by prior venous distension produced a RHBF of 52.4 cc. This difference was not considered significant.

**DISCUSSION**

**Vasodilator Metabolites.** Lewis² ascribed reactive hyperemia to a non-volatile vasodilator metabolite. He postulated that this material was formed constantly, thus accumulated in the tissues during circulatory arrest. The basis for this theory was his observation that the intensity of reactive hyperemia was directly related to the duration of arterial occlusion. This evidence seemed to implicate a vasodilator substance whose concentration was increasing with time, rather than the hemodynamic alteration (presumably rapid) which followed circulatory arrest. Finally, noting the similarity between the diffusing redness of histamine wheals and the red flare surrounding a local area of skin subject to prolonged ischemia, Lewis concluded that the material responsible for reactive hyperemia was at least similar to histamine and referred to it as "H-substance."

Using a biological assay method, Barsoum and Smirk⁶ found a direct relationship between the concentration of histamine in the venous blood drawn at the conclusion of circulatory arrest and the duration of the circulatory arrest. Utilizing a system of cuffs on the forearm, Lewis and Grant⁶ were unable to demonstrate a high concentration of intravascular "H-substance" or other vasodilator material. Thus, they considered it to be slowly diffusible. Further, Kwiatkowski⁷ could not repeat the observations of Barsoum and Smirk referred to above. More recently, unsuccessful attempts have been made to depress reactive hyperemia blood flow with the administration of anti-histaminic drugs.⁸ However, the same doses of these drugs did reduce the vasodilatory effects of exogenous histamine. It has also been shown that desensitization of an animal to histamine does not reduce reactive hyperemia blood flow.⁹

Stoner and Green¹⁰ found a slightly increased concentration of adenosine triphosphate (A.T.P.) in venous blood obtained at the conclusion of 30 minutes of circulatory arrest in man. Also doses of A.T.P. of the same order of magnitude produced vasodilatation, an observation confirmed in animals by Folkow and associates.¹⁰

Concerning metabolic factors in general, the following observations are pertinent. Total reactive hyperemia blood flow seems to be dependent upon the level of metabolic activity, as altered by local temperature changes, at low (14 C.) and normal (32 C.) temperatures, but is less than would be expected on this basis at high (43 C.) temperatures.¹²

We have observed that brief periods of increased metabolic activity of muscle (exercise) during relatively long periods of arterial occlusion introduced a powerful vasodilator factor. This factor was not related to the time when increased metabolic activity occurred during the occlusion. The exercise was not judged to be of sufficient intensity to cause release of epinephrine into the general circulation thereby producing muscle vasodilatation, as it produced no local symptoms nor did alterations of pulse or blood pressure occur. The effective intravascular pressure was low as a result of arterial occlusion, thus any further reduction brought about by increased tissue pressure during the brief exercise period could hardly account for the markedly increased RHBF. One is left with the explanation that the exercise increased the elaboration of a vasodilator metabolite. It seems likely that the metabolite which is produced by muscular exercise might also be produced in small quantity by muscle maintaining normal tone at rest. Thus the vasodilatation of reactive hyperemia in the resting arm might also be accounted for in part at least by a vasodilator metabolite.

**Intravascular Pressure.** Bayliss³ suggested that the sudden removal of local arterial pressure, which had been a direct mechanical stimulus for producing "vascular tone," caused vasodilatation. In contrast to Lewis, he felt that the short duration of arterial occlusion...
(five seconds) adequate to produce reactive hyperemia could not result in a significant accumulation of vasodilator substances. Further, he observed that smooth muscle, from other sites, tended to lose tone when mechanical stimuli were removed. He also found that rises in arterial pressure produced by sciatic or splanchnic stimulation resulted in vasoconstriction. This latter observation may have been influenced by his failure to adrenalectomize the animals or to sympathectomize them. Folkow observed that release of arterial occlusion produced a much greater reactive hyperemia flow than did release of venous occlusion of the same duration. He concluded that reactive hyperemia could be accounted for on the basis of intravascular pressure changes alone.

We attempted to evaluate the role of intravascular pressure as a factor producing reactive hyperemia by maintaining a mean intra-arterial and intra-arteriolar pressure at a high level during arterial occlusion. The RHBF was reduced to a significant degree by this procedure (approximately 21 to 51 per cent) but reactive hyperemia was by no means abolished by the more normal mean intra-arterial pressure during occlusion. The role that the increased volume of blood present in the extremity played in the reduction of RHBF was evaluated. This increased volume of blood in the extremity was maintained, but with a low effective intravascular pressure (by raising external pressure) with the result that RHBF was essentially the same as that produced by an equivalent arterial occlusion alone.

These observations seem to indicate that intravascular pressure does play an important role in the production of reactive hyperemia. However, they also indicate that a low intravascular pressure is not the sole cause or even the predominating cause of reactive hyperemia. The reactive hyperemia of exercise was unaffected by maintenance of intravascular pressure alone.

**Blood Flow “Debt.”** Abramson and co-workers observed that RHBF of forearm and leg segments was approximately equal to the calculated blood flow “debt” incurred during arterial occlusion. These observations were made at a plethysmographic temperature of 32°C as well as at temperatures of 10 to 14°C. Periods of occlusion ranged from three to 12 minutes. We were unable to repeat these observations. In every instance except two the RHBF exceeded the calculated blood flow “debt.”

**Conclusions**

The possible relationship of vasodilator metabolites and of intravascular pressure fall to reactive hyperemia was studied.

Metabolic activity of muscle results in vasodilation due to the production of vasodilator metabolites. It is not unreasonable to assume that these metabolites are produced by muscle at rest, but in smaller concentrations than during exercise. The major portion of the vasodilatation of reactive hyperemia is probably due to the accumulation of these vasodilator metabolites.

A fall of intra-arterial pressure plays a significant but lesser role in the mechanism of reactive hyperemia of resting muscle. This role appears to be insignificant in the reactive hyperemia following exercise performed during arterial occlusion.

Calculated blood flow “debt” during simple arterial occlusion is greatly “overpaid” by the total reactive hyperemia blood flow under the conditions of our study.

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The Role of Atrial Contraction in Left Ventricle Dynamics

It has been held that the contribution of left atrial contraction to ventricle efficiency can be evaluated in complete heart block because the relation of atrial to ventricular contraction changes from beat to beat. Such studies (e.g., Gesell, Am. J. Physiol. 40: 267, 1916) have indicated that the efficiency of left ventricle contraction depends significantly on a proper timing of atrio-ventricular sequence.

Recent studies on patients with complete heart block strongly suggest that interpretations are complicated by the fact that the stroke volume of the right ventricle is simultaneously affected by variable $A_sV_s$ intervals, with the result that variable volumes of blood are delivered to the left heart and so influence its stroke volume in succeeding beats.

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