EFFECT OF EMBARRASSMENT ON BLOOD FLOW TO SKELETAL MUSCLE

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PHILADELPHIA

Effect of Embarrassment on Blood Flow to Skeletal Muscles

Some emotions are associated with an increase in blood flow to the limbs. In 1938 I inadvertently demonstrated this to the Medical Research Society in London; I had intended to show the effects of an epinephrine infusion, but my subject was so perturbed and his forearm blood flow so persistently increased, that I was unable to show any additional effect of epinephrine.[1] Judging by my feelings at the present moment, the circulation through my own limbs is in much the same state.

The usual explanation of the mechanism of the increase in limb blood flow, given, for example, in Dr. John Shepherd's excellent book on the circulation in human limbs[2] is: the increased flow takes place in the muscles and not in the skin, it is in part due to sympathetic vasodilator impulses which are cholinergic, and in part to a humoral agent, probably epinephrine. Since the book was published, additional knowledge has become available and permits different deductions.

Methods and Presentation of Data

The emotional stimulus I have used is to ask the subject a question in mental arithmetic and then to heckle him as he tries to give an answer. It is the emotional response to the heckling rather than the performance of mental arithmetic which stimulates the increase in the blood flow to the limb. When the interval between stimulus and response is to be timed, I have used a sudden loud noise to produce a "startle" reaction. These two stimuli appear to cause the same type of somatic reaction but other so called "strong" stimuli[3] may provoke a vaso-vagal or other reaction, and if so the results would not be relevant to the present question.

Blood flow has been measured by the plethysmographic methods.[4] Figure 1 shows two examples in which the blood flow was measured

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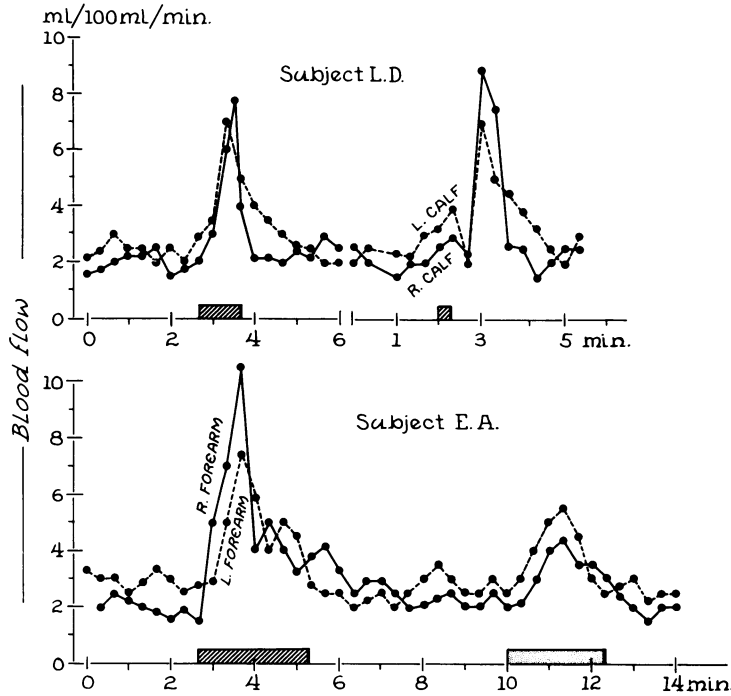

FIG. 1. Upper graph bilateral calf blood flows. The shaded blocks on the base line represent the interval between the asking of a question and the reply. Lower graph bilateral forearm flows. The shaded block as in the upper graph. The stippled block is the presumed duration of a spontaneous emotion.

bilaterally. It demonstrates that the size of the response is not constant and that it is unpredictable, so that to compare its size before and after giving a drug or carrying out a procedure is unsatisfactory. The effect of a drug or procedure should be limited to one limb and the response in the limb then compared to that in the opposite limb which has been unaffected by the procedure. Since responses in the two limbs are qualitatively rather than quantitatively the same, a procedure must result in large and constant differences if we are to be convinced of its effect. It is often difficult to decide how responses in the two limbs should be compared, particularly if the drug or procedure significantly alters the level of "resting" blood flow in the limb. I have made comparisons by calculating the ratio of mean blood flow during the response in the experimental arm to the mean blood flow during the same time in the control arm. Other workers[3, 6] have compared the *differences* between the level of "resting" blood flow and the level of blood flow during the

response on the two sides. I doubt that this comparison is justifiable because observations such as are shown in figure 1 do not indicate that the level of blood flow during the response is related to the resting level, nor does it seem logical to compare the differences in blood flow levels when the drug or procedure has itself effected a marked change in "resting" blood flow level. When I have used the data of these workers, I have recalculated it as the simple ratio of mean blood flow during the response in the two arms. In the case of observations on the effect of block of cutaneous nerves in one forearm this difference of comparison led to a deduction contrary to that which the workers had made from their own data.[3]

Cholinergic blockade of a forearm has been achieved by infusion of atropine solution into the brachial artery.[3] In some experiments cutaneous circulation was suppressed by means of epinephrine iontophoresis.[5]

Neurogenic Influences

Sympathectomy: I had expected that sympathetic vasomotor nerves would be active in the response, but was surprised to find that as large a response could be obtained in a sympathectomized limb as in a normal limb (Fig. 2). Pharmacological blockade of the adrenergic impulses by bretylium tosylate was also without effect on the response. Others, notably Barcroft, Brod et al[6] have found sympathectomy whether by surgery or paravertebral block to be without effect on the response. Wilkins and Eichna[7] are quoted as having produced evidence that the

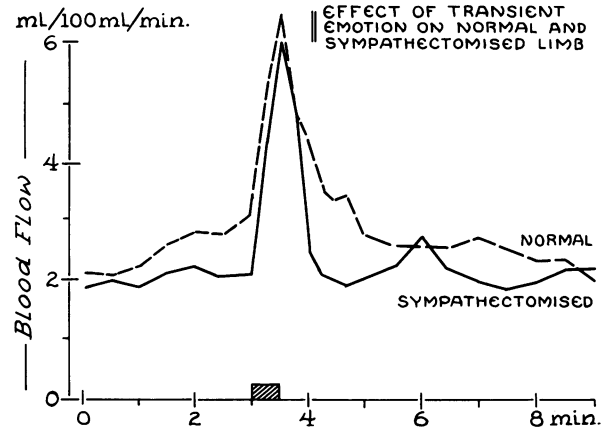

Fig. 2. Bilateral calf blood flows showing changes associated with mental arithmetic. One normal leg, the other three months after lumbar sympathectomy.

sympathetic nerves are implicated, but reference to their paper shows that the major response persisted after sympathectomy. Blair et al[3] give a figure, which is reproduced by Shepherd[2] in which there is a large response in the normal limb, but no response in the sympathectomized limb; this result, however, is not indicative of their results in other sympathectomized limbs. The evidence indicates that impulses passing through the sympathetic ganglia are not active in the response.

Denervation: I have not personally observed the effect of denervation on the response but Wilkins and Eichna[7] observed a response in the leg during spinal anesthesia, and Blair et al[3] found the response still to occur in a forearm of which the deep nerves had been anesthetized at the elbow. The latter workers remark that the *increase* in blood flow during the response was less in the forearm with blocked nerves than in the normal forearm, but this observation is hardly relevant since denervation had resulted in a higher level of "resting" flow, and during the response the level of flow was equal in the two arms. These workers also report a single experiment in which the flow in the normal arm exceeded that in the denervated arm, which suggested that vasodilator nerves were active. However, in this instance the stimulus was not mental arithmetic but a so called "strong" stimulus consisting of revolting suggestions with the aid of a recently killed rabbit. Since this stimulus is comparable to those which have been used to promote vaso-vagal attacks, this single observation may have been a confirmation of Barcroft and Edholm's demonstration[8] that vasodilator nerves are active in vaso-vagal attacks, and not relevant to the response to mental arithmetic.

Cholinergic Vasodilator Impulses: It has been reported[3, 6] that cholinergic impulses, vasodilator to skeletal muscle, are implicated in the response. On animal experiments[9] such impulses are prevented by sympathectomy, and because the response may be elicited after sympathectomy in man it would seem unlikely that this mechanism is implicated.

The possibility of activity of cholinergic impulses was investigated by carrying out a cholinergic block on one forearm and then comparing the responses in the two forearms. In figure 3 the results of three groups of workers are given. On the left are the results of experiments done in Belfast,[3] in the middle my own results obtained in London, and on the right results of Barcroft et al[6] from Prague. Bearing in mind the possible spontaneous differences in response in the two arms, the results fail to indicate any strong effect of the cholinergic fibers, though a closer look aroused the facetious thought that the effect of the cholinergic impulses becomes weaker as we go East, that is from left to right. A more likely explanation of this difference is that in Belfast and London younger

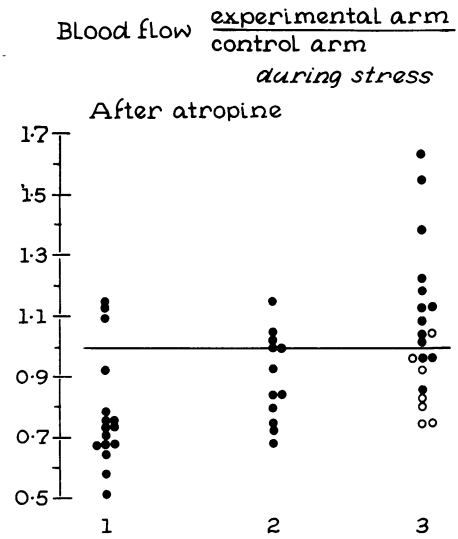

FIG. 3. Ratio of mean forearm blood flows during stress (mental arithmetic). One forearm with cholinergic block (atropinized) the other normal. Results of three groups of workers I. Blair et al (3) II. Holling unpublished III. Barcroft et al (6).

subjects were used than in Prague. If the younger subjects in the Prague group are differentiated (open circles) it appears that it was in them that the cholinergic impulses were active. This observation reminded me that Grant and I[10] had thought that cutaneous circulation was more active in youth, and led me to re-examine the possibility that the cholinergic impulses might be acting on the cutaneous circulation. Allwood et al[11] had shown, at least in the hands, that there was sometimes a cholinergic cutaneous vasodilator response to mental arithmetic. I carried out more observations on the effect of emotion after cholinergic block of one arm, but with the cutaneous circulation to both forearms blocked by means of epinephrine iontophoresis. The results of these experiments are shown in the right hand column of Fig. 4. The responses were equal in the two forearms, which is consistent with the proposition that the cholinergic impulses act on the cutaneous circulation. More positive evidence is available from a re-examination of the data obtained by Blair et al.[3] They had measured the response in the two forearms after procaine block of the cutaneous nerves to one, and they considered that the results showed that the response was "not regularly affected, and on the average unaltered" by the cutaneous block. The data of these experiments has been recalculated as the ratio of the mean blood flow during the response in the arm with blocked cutaneous nerves to the same

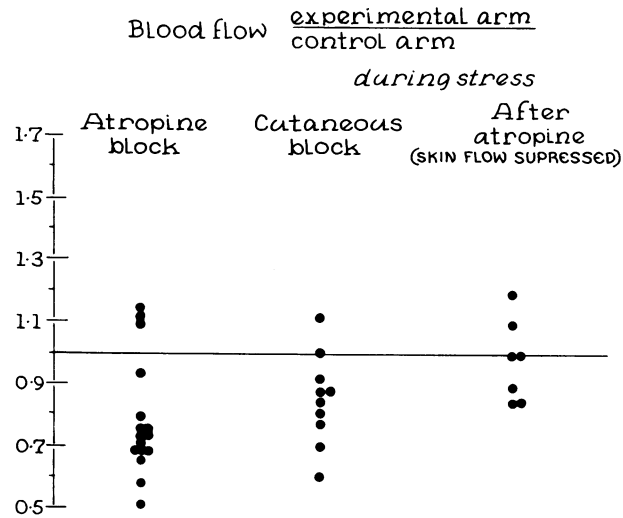

FIG. 4. Ratio of mean forearm blood flows during stress (mental arithmetic). Left column: repeat of left column in Fig. 3. Middle column: experimental arm with procaine block of cutaneous nerves at elbow, opposite arm normal. Right column: suppression of cutaneous circulation in both forearms, cholinergic block in addition in experimental forearm.

measurement in the opposite normal arm, and is shown in the middle column of Fig. 4. The left hand column is the data of these workers on the effect of cholinergic block, just as is shown in the left hand column of Fig. 3. It appears that the response in the experimental arm is as much diminished by block of the cutaneous nerves as it is by cholinergic block. The evidence that the cholinergic vasodilatation takes place in the cutaneous circulation is at least as convincing as that it takes place at all.

HUMORAL EFFECTS

Since neurogenic impulses do not appear to be involved in the increase in blood flow to skeletal muscle, hormonal mechanisms should be considered.

Epinephrine was previously considered as the most likely hormonal substance to cause this effect, so it was disconcerting to find that a response could be obtained still after denervation[7] or removal[6] of the adrenal glands. It is true that the response in the latter instance was said to be diminished, but since the magnitude of the response is unpredictable it is unlikely that this comment could be substantiated. I was unable to provoke any response in three patients who had been

TABLE 1

Embarrassment	Epinephrine	Dopamine		Isoprenaline	
		(18)	(20)	(19)	(10)
Increase in Muscle Flow					
Sustained (1)	Unsustained (1) (16)	Sustained		Sustained	
Skin Flow (Hands and Face)					
Little Change (3)	Marked Decrease (17)	Little Change		Brief Dilatation	
Change in Diastolic Blood Pressure					
Small Increase (14)	Small Decrease (1)	Small Decrease		Large Decrease	
Increase in Blood Sugar					
Small (15)	Large	Small		Large	

adrenalectomized for hypertension, but I believe that they experienced no stimulus because they were uninterested in answering mental arithmetic. Additional evidence against participation of epinephrine is afforded by the action of Dichloroisoprenaline, which blocks the peripheral vasodilator effect of epinephrine in man[12] but does not uniformly block the vasodilator response to "strong" emotional stimuli.[13]

Within recent years our increased knowledge of physiological actions of different catecholamines has shown that they have a spectrum of different actions. In Table 1 some of the somatic effects of embarrassment are compared with those of the catecholamines, epinephrine, isoprenaline, and dopamine; norepinephrine has not been included in this comparison since its action of the blood vessels of skeletal muscle is constrictor. The sustained increase in muscle blood flow which occurs in emotion cannot be reproduced by epinephrine infusion but may be by either dopamine or isoprenaline. Epinephrine causes marked vasoconstriction of the skin of the hands and face, but such constriction is neither seen with emotion, nor with isoprenaline or dopamine. All these catecholamines cause some increase in systolic blood pressure, as does emotion, but their effects on diastolic pressure differ. Emotion is often associated with a small increase in diastolic pressure, whereas isoprenaline produces a marked fall; with epinephrine there is usually a slight fall of diastolic pressure, but with dopamine the change is slight, either a rise or a fall. Blood sugar is little affected by emotion, and

this is true also of dopamine. In contrast the well known glycogenolytic properties of epinephrine are shared by isoprenaline. Dopamine, therefore, is the catecholamine whose effects most closely resemble those of emotion.

We usually think of dopamine only as a precursor of norepinephrine, but the possibility of ascribing a physiological action to it is not new. Indeed Allwood and Ginsburg[20] suggested that it might be associated with the response to fright because it is the only catecholamine to be associated with piloerection on arterial injection.

Since the presumed hormone does not appear to be secreted from the adrenal glands, the problem of what is its point of entry into the blood stream remains.

In the response to a sudden loud noise, the "startle" reaction, the major increase in blood flow to the forearm occurs at about 30 seconds, which is about half the interval between the injection of epinephrine and the subsequent increase in blood flow (Fig. 5). Does the shorter effective appearance time indicate that the hormone takes a shorter path in the circulation, as if it were coming from the heart or lungs? It is known that there are stores of norepinephrine in the myocardium which may be released into the circulation, but it is not known whether other catecholamines are so released.[21] It is also known that more than 90% of the catecholamine content of the lungs is dopamine, which appears to be stored in a special type of chromaffin cell.[22] So there exists a histological appearance in the lungs which requires a physio-

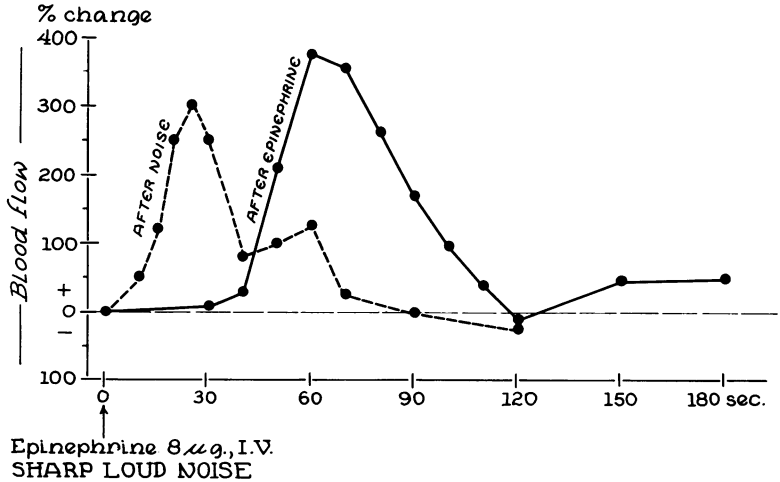

FIG. 5. Forearm blood flow following (a) sudden loud noise (b) intravenous injection of 8 micrograms of epinephrine (mean of 8 observations).

logical function, and a physiological function which requires a source. Future work is required to decide whether the two requirements can supply each other.

Summary

Embarrassment provoked by heckling during the performance of mental arithmetic is associated with an increase in the blood flow to skeletal muscle of the limbs. The vasodilatation is not directly mediated by nervous impulses, though cholinergic vasodilatation in the cutaneous circulation of the forearm may occasionally occur. The vasodilatation in muscle appears to be mediated by a humoral agent. Review of the actions of catecholamines indicates that dopamine is more likely to be the agent concerned than epinephrine, norepinephrine, or isoprenaline. The hypothesis is suggested that dopamine enters the blood stream from stores in the lungs.

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DISCUSSION

Dr. Lewis Dexter (Boston): This has been a very nice paper. I would like to ask Dr. Holling one question. Does the increased muscle flow serve any metabolic function?

The reason I ask this is that during cardiac catheterization, which is hardly a quieting procedure, there is usually a definite increase in cardiac output. This is best eliminated by having the patient exercise previously to eliminate his apprehension. Five minutes later, one gets almost basal figures for his flows and pressures. It's one way of getting an essentially basal state. Although I have never measured muscle flow under the circumstance of apprehension, there is a narrow A-V O_2 difference and minimal increase of O_2 consumption indicating that O_2 utilization is not increased. I have always assumed that there might be a large muscle flow because muscles are by far the biggest organ of the body. If this is true, the increased flow would not subserve any metabolic function. I wonder if Dr. Holling would comment on this.

Dr. Stewart Wolf (Oklahoma City): I wonder if Dr. Holling has encountered under other kinds of circumstances the opposite effect? He has isolated a certain kind of situation which yields a predictable reaction. Any bodily mechanism may participate in a reaction to a meaningful situation which may have emotional significance to the individual. The example that he gave, blushing, of course is matched by the opposite, pallor of the face under different kinds of emotional situations. Emotion doesn't do anything uniform to the body. The evidence indicates that all of the equipment of the body may, under certain circumstances, be mobilized into a pattern of response to a meaningful situation. I wonder whether, in the course of Dr. Holling's experiments, there might not have been introduced other kinds of situations which might have led to a decrease in muscle blood flow associated with emotional stress.

DR. TIMOTHY R. TALBOT, JR. (Philadelphia): I wonder if I could throw a sort of personal application into Dr. Wolf's comments? I once had pericarditis, and therefore learned, under the most astonishing variety of circumstances, what the things are that make one's cardiac rate change and what creates pain in a pericardium or around it, things like stop lights, and all of the variety of things you would never suspect, that you encounter thousands of times in a day. Are you provided with a signal to make you aware of your own instability? I don't know. But quite clearly, these things occur, such as anger, fear, anxiety, and the like. I think this might be an extremely interesting subject for prolonged discussion. But I am worried about your word "emotion."

DR. CHESTER M. JONES (Boston): I would like to add what I was hoping Dr. Wolf might mention. We observed a combination of changes in the colonic mucosa in a similar event taking place under sigmoidoscopic examination in a normal subject subsidized for the purpose, and we had what we call a "rectal blush" which was just as extreme as if noted in the face. I'm sure that this is a general effect rather than just a localized one in the skin or any other single area. It happened in about fifteen seconds, actually when the patient was very embarrassed by the nurse coming into the room while the patient was in the knee-chest position.

DR. HOLLING: I know that Dr. Dexter is familiar with Dr. Cannon's theory that an increase of blood flow such as I have described is in preparation for flight or fight. However helpful it may be for these purposes I can assure you that it doesn't seem to be any help at all when giving a talk to an audience such as this. I have measured the oxygen content of venous blood from the muscle under these circumstances and found that it is pretty nearly arterial. Others have studied sugar, phosphates and potassium without finding that any metabolic process is stimulated by the increase in blood flow.

I am glad that Dr. Wolf brought up the subject of what is meant by emotion, and I should apologize for my free use of the term. The literature on this subject is bedevilled by the failure to distinguish between the different somatic reactions to different emotions. I have in mind a group who applied what they termed "strong stimuli" to provoke the response of which I have been talking, but it is more likely that they provoked the very different response of a vaso-vagal reaction. I do not know whether other emotions such as fear, anger or anxiety cause somatic reactions different from that which I have studied. Dr. James Warren is studying anger and fear in patients under hypnosis and finds that these two emotions provoke the same type of cardiac response.

Dr. Talbot's comment reminds me that I have noticed in myself a brief but definite delay between an alarm (such as a near accident in traffic) and the ensuing tachycardia and trembling; but perhaps such responses differ in different people. Concerning Dr. Jones and his rectal blush, I have made no comparable observations during mental arithmetic. His findings, however, are like those which Alexis St. Martin made at the other end of the alimentary canal.