

PHYSIOLOGIC PROBLEMS IN PERIPHERAL VASCULAR DISEASE*

HEBBEL E. HOFF, M.D. †

Houston, Texas

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CIRCULATION THROUGH MUSCLE

The expanding employment of sympathectomy in the treatment of a variety of occlusive and vasospastic conditions has not occurred without objectors, and one of the most vocal has been Cohen (49) in his Hunterian lecture on "Traumatic Arterial Spasm." He wrote, "It has become customary to regard the sympathetic as having an adverse influence on the return of the circulation after vessel ligation in that it holds the collaterals in so-called spasm. The sympathetic system is said to keep the limb cold, and physiological 'release by plexus block' or sympathectomy has therefore been urged. It is important to discuss this view for it enters largely into the treatment of the limb with vessel in spasm. Considerable evidence is accumulating, as Freeman (50) points out in a review of peripheral circulation, that the circulation of the skin and muscle may be independently regulated, that changes occur in the skin with opposite or no changes in the muscle. Friedlander (51) and his associates observed that neither paravertebral block, spinal anesthesia, nor reflex heat dilatation increases the muscle circulation though they always increase that to the skin. Kunkle and Stead (52) in a study of peripheral vascular diseases have pointed out also that a normal blood flow to the foot does not rule out inadequate circulation to the muscle of the calf. The sympathetic system by its control of the cutaneous circulation is of great importance I think in the anemic limb for it prevents the pooling of blood in a relatively unimportant area. The trauma that injures the vessel may sever or damage the main peripheral nerves, and therein the sympathetic fibers. The cutaneous dilatation that follows this vasomotor paralysis may not be without danger, and may be the determining cause of the underlying muscle death—the Volkmann lesion. Putti (53) reported in 1938 that he had to operate on 44 nerve lesions in 58 Volkmann cases. Thomas (54) in

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† From the Department of Physiology, Baylor University College of Medicine, Houston, Texas.

1909 reviewing Volkmann's contracture reported nerve lesions in 60 per cent of the 107 cases. Griffiths (55) reported that 10 out of 13 of the severe Volkmann cases in his series had lesions of the peripheral nerves. From the experience in the last war, Makins (56) reported that injuries to the nerves, especially the median in the upper extremity and the internal popliteal in the lower, favored gangrene. Thus we see that the cold limb said to be due to spasm of the arterial collateral circulation is in fact a protective measure and to dilate the skin vessels by forced heating or sympathectomy may not be helpful. What avail if we save the skin and lose the muscle?"

The idea that the innervation of the vessels of the muscles is different from that of the skin or intestine arises from the work of Heidenhain and Grützner (57) in 1877, who found that stimulation of a centripetal nerve, for example the radial, or saphenous, evoked vasodilatation in the muscles of the thigh. Much additional work both in relation to nerve stimulation and to the effect of epinephrine which actively dilates the vessels of the muscles has shown that this view has an element of truth in it, and the sympathetic chain of many experimental animals contains vasodilator fibers which are cholinergic (58, 59, 60). This is particularly so in the dog. On the other hand, the rabbit has few sympathetic vasodilator fibers to the muscle, while the hare has a great many. When vasodilator substances are injected, the difference between hares and rabbits is very striking. With acetylcholine and epinephrine, excellent dilator effects are obtained in the muscles of the hare but almost no dilatation in the muscles of the rabbit. Burn (61) examined the muscles of the monkey by the same method and found no vasodilator fibers in the sympathetic chain. Even after large doses of ergotoxine, which is supposed to reverse the action of epinephrine so that it becomes depressor and vasodilator, sympathetic stimulation still produced vasoconstriction in this animal. Furthermore, it was found that acetylcholine had little or no dilator activity.

The differences observed in five species, rabbit, monkey, cat, hare and dog, are useful indications of the importance of sympathetic vasodilator fibers to the vessels of the muscles. The fibers are absent in the rabbit and the monkey, demonstrable only with difficulty in the cat, and at once evident without the use of drugs such as ergotoxine or eserine in the hare and in the dog. In the cat it is the depressor effect of epinephrine, and not the vasodilator effect of sympathetic stimulation, which is most easily seen after ergotoxine has been given. This effect is relatively small. It is thus apparent that animal experiments afford no ready guide to the possibility of vasodilator or vasoconstrictor fibers in the human muscle.

Recently, Stein, Harpuder and Byer (62) pointed out that sympathetic denervation of human limbs increased the blood flow to the skin, while in the muscular area such as the calf or forearm the flow remained relatively unchanged. Heating, muscular exercise, or pe-

riods of vascular occlusion followed by release produced substantial increases in muscle blood flow. Their conclusion was that local metabolic needs play the dominant role in determining blood flow in muscle. Later it was shown that epinephrine injected into the brachial artery in the normal forearm had a dual effect upon blood flow. With fractions of a gamma the flow increased. With doses of several gamma it was diminished. It was concluded that with small doses of epinephrine or with low intensity of sympathetic stimulation vasodilatation is produced, and with larger doses of epinephrine or stronger sympathetic stimulation vasoconstriction results.

Further observations on the sensitivity of blood vessels to epinephrine after the usual type of lumbar sympathectomy in man indicate again that there are both constrictor and dilator mechanisms in muscle vessels and only constrictor mechanisms in skin vessels in response to epinephrine (63). This conclusion is in conformity with the earlier experiments in the cat by Grimson and Shen (64) who showed that after injection of small doses of epinephrine both a skinned and a normal limb will respond by vasodilatation, while with larger doses of epinephrine vasoconstriction is produced.

Recently Barcroft and Edholm (65, 66) have reviewed the evidence for a vasoconstrictor tone in vessels to human muscle. They called attention to the fact that Grant and Holling (67) found that blood flow in the forearm of human beings could be increased by heating the legs or the body, and that Wilkins and Eichna (68, 69) obtained a similar increase in blood flow, suggesting that vasodilatation had occurred. Barcroft and Edholm (65, 66) carried out this procedure in a large number of subjects in whom the forearm was put in warm water, and found a considerable increase in the blood flow to the forearm when the legs were heated. The effect is absent in sympathectomized subjects. Further evidence came from an unexpected finding in the course of studies of blood flow in the forearm during fainting after venesection. In one of the early experiments, the subject fainted and, to the surprise of the investigators, the blood flow in the forearm was much increased during the faint despite the sudden decrease in blood pressure. During this time measurements of cardiac output by the direct Fick method showed that cardiac output did not decrease during the fainting. They concluded that fainting is not a cardiac syncope but represents a peripheral failure, that is, fall in blood pressure due to peripheral vasodilatation. When subjects were tested following sympathectomy which was established to be complete, it was found that the blood flow to the forearm during rest was within normal limits as in all cases the sympathectomy had been performed some time previously, and as Grant (70) and others have shown, forearm blood flow is only temporarily increased after sympathectomy, the vessels soon recovering their tone. In these subjects blood flow to the forearm did not increase during fainting. On the contrary, blood flow diminished as the blood pressure

fell and recovered when the pressure rose again. This provided definite evidence that the dilatation in normal subjects was not due to the secretion of epinephrine or any other humoral agent, for such an effect would still have been present after sympathectomy. On the other hand, since the dilatation was abolished when the vasomotor nerves were absent, it was evident that the dilatation was mediated by the vasomotor nerves.

A striking feature of this type of syndrome is the intense pallor of the skin during the faint, and it appeared unlikely that the considerable increase in blood flow could be taking place in the skin vessels. This was investigated by comparing the blood flow in the hand and forearm. The hand consists largely of skin and bone; only 15 per cent is muscle. If the vasovagal dilatation takes place in the muscle vessels only, the rate of flow through the hand should diminish during the fainting, and this did occur. Weiss and others had shown previously that during the circulatory collapse induced by amyl nitrite, a collapse which closely resembles fainting, the blood flow to the hand may be unrecordable. In the hand as a whole, there is no doubt that blood flow decreases during fainting, so it was concluded that during fainting induced by hemorrhage there is a sudden vasodilatation in muscle blood vessels owing to nervous impulses.

This conclusion led to the next question. Was the dilatation due solely to the removal of vasoconstrictor tone or did active vasodilatation occur? Experiments were carried out on subjects in whom a nerve block was performed in one arm. This procedure removes vasoconstrictor tone and therefore increases the rate of blood flow in the forearm; it would presumably also block vasodilator fibers. When fainting was induced in these subjects, the blood flow decreased as the blood pressure fell, similar to its behavior in the sympathectomized arm, but during the faint the level of blood flow was much less than in the normal arm. In considering the condition in the two arms, one with a nerve block and the other intact, in the first, vasoconstrictor tone had already been removed by the nerve block. If the vasodilatation during the faint was due solely to the removal of vasoconstrictor tone, then the condition in the two arms during the faint should be the same: that is, in the one arm vasoconstrictor tone was removed by nerve block before the faint and in the other, it was removed by fainting. The flow in the normal arm at this stage, however, was much greater than in the arm with the nerve block, so this increase could not be caused only by the removal of vasoconstrictor tone. During fainting the increase in blood flow in the forearm cannot be entirely explained by removal of vasoconstrictor tone. The only reasonable conclusion is that the additional vasodilatation was mediated by vasodilator nerves. Thus Barcroft and Edholm (66) concluded that there are both sympathetic vasodilator and vasoconstrictor fibers to human muscle, that in normal circumstances a vasoconstrictor tone exists in these muscles, and that sym-

pathectomy, because it removes the vasoconstrictor tone, may temporarily, at least, increase the blood flow to the muscles themselves. Their experiments recall Hunter's (71) observation of a patient who fainted during venesection and in whom the blood flowing from the incision became bright red during the faint. They pointed out that the existence of sympathetic vasoconstrictor tone in muscle does not imply that section of the nerve fibers concerned will be followed by permanent vasodilatation, and as Grant and Holling (67) have shown, the forearm is only hyperemic for about a week after sympathectomy. It is noteworthy that the increase in blood flow during exercise cannot be explained by the release of sympathetic tone in blood vessels to muscle. Release of sympathetic tone in the body musculature would probably increase its blood flow by about 1.5 liters a minute, but in strenuous exercise the increase is probably nearer 20 liters. This accords with the established teaching that the hyperemia in active muscles is largely brought about by the action of metabolites.

CUTANEOUS ARTERIOVENOUS COMMUNICATIONS

Another apparent complication of sympathectomy calls attention to a further function of sympathetic control of peripheral vessels. Atlas (72-75) reported experience with 3 patients after lumbar sympathectomy in whom this procedure, although producing an elevation in the surface temperature of 2 to 5 C. above the control level, was followed rapidly by gangrene, necessitating amputation of the leg in each case. Atlas attributed this disaster to the opening of arteriovenous communications which, although they permitted the surface temperature to rise, actually resulted in still further reduction in the nutrient capillary flow, for the quantity of blood which can be delivered to peripheral tissues in a given period of time depends not only upon the diameter of the arteries supplying the part but also upon the peripheral resistance. Lowering the peripheral resistance in any section of the vascular bed proximal to the nutrient capillaries, and especially those in the distal portion of the extremity, necessarily reduces the effective capillary pressure. The effect upon the height of oscillation, measured at the ankle, of lowering the peripheral resistance by opening up of blood vessels in the working calf muscles had been previously reported, and it was suggested at that time that extensive sympathectomy might be contraindicated in the presence of advanced obliterative disease, since the peripheral resistance might be so lowered in the proximal portion of the limb as to curtail the flow of blood in the more distal parts. At approximately the same time that Atlas (72-75) reported his experiences, Freeman, Leeds and Gardner (50) noted a curious phenomenon in 4 patients, the significance of which had not been appreciated. The first patient was suffering from thromboangiitis obliterans and had sustained an occlusion of the left iliac artery. Immediately after lumbar ganglionectomy the hypesthesia of the left foot, presumably of an

ischemic nature, became much more extensive. At the time it was thought that the decrease in blood pressure during spinal anesthesia and the use of the head-down position to combat this complication accounted for the manifest increase in vascular insufficiency. Some months later, however, extensive gangrene of the dorsum of the foot developed, which required amputation of the leg. The fact that the patient had continued to smoke and presumably had further evidences of arterial obliteration served to explain the development of gangrene, although the distribution of the necrosis on the dorsum of the foot while the toes were still viable was curious. When the same event occurred in other patients with advanced obliterative arterial disease, it was concluded that the sympathectomy itself had contributed to the bad results, and attention was called to the function of the peripheral circulation in the regulation of body temperature. In accordance with the requirements for conservation or dispersal of heat, circulation to the extremities is reduced or expanded.

The anatomic structure involved is apparently the neuromyo-arterial glomus of Sucquet (76) and Hoyer (77). Glomera have been described by Popoff (78) both in normal skin and in individuals suffering from thromboangiitis obliterans; they provide a direct passageway from the arterial tree to the venous side of the circulation without perfusing the capillary bed. The efferent arterioles to these structures are normally held in a state of constriction by sympathetic impulses and, as the studies of Clark (79); and Grant, Bland and Camp (80) have shown in the rabbit and in human skin, blood can be shunted rapidly from the arterial to the venous system to modify the circulation through the skin and thus regulate heat loss.

Grant (67) and others, however, have shown that although this mechanism is apparently of value in the vasodilatation that follows mild heat-loss stimuli, such as moderate warming of the body, generalized arteriolar vasodilatation which involves capillary flow occurs when the demand for heat loss is at all significant. Therefore, the flushing that accompanies sympathectomy is a combination of relaxation of arterio-venous communications and of the normal arterial-capillary-venous network. It is certainly difficult to answer the objections of other investigators who point out that the gangrene that develops in these cases may be the result of further development of the disease, but it may well be that in certain stages this type of cutaneous vasodilatation might be a critical factor, particularly in circumstances in which there is extensive obliterative occlusion with a minor vasospastic element, so that the deviation of blood through these channels might overbalance what relaxation of the other arterioles had been effected by sympathectomy.

TRAUMATIC ARTERIAL SPASM

John Hunter had a very simple explanation of traumatic arterial spasm, namely that an injured vessel has a natural disposition to con-

tract. An understanding of this natural disposition of the smooth muscle of the arterial wall is a great aid in explaining the apparently peculiar responses of the vessel (71). Smooth muscle responds to a greater variety of stimuli than does skeletal muscle. It responds to stretch, whereas skeletal muscle does not. Rapid stretching is always a more effective stimulus than slow stretching. We can appreciate, therefore, why manipulation of a fracture or the "near miss" of a vessel by a gunshot or bomb splinter may initiate spasm. When smooth muscle contracts, the fibers may decrease to a sixth of their resting length. The major peripheral vessels may contract till they appear to be a mere thread, and may be maintained in this state even when the tissues around are dead or dying, for smooth muscle maintains its new length with very little increase in its oxygen consumption and without rapid fatigue.

The behavior of smooth muscle at times appears bizarre. It has been noticed that often a mechanical stimulus which causes a contraction when applied to a muscle which is in a state of slight tonic contraction evokes relaxation when the tone is great. Thus, in attempting to suture a divided vessel, the contracted ends at first appear to make this impossible, but as gentle traction is applied by means of the stay sutures, the vessel wall relaxes. Such spasms exist not only at the point of trauma, but may extend throughout the distal arterial tree (81). Thus Cohen (49) quoted the case of the American soldier who fell from a building, and fractured the humerus in the middle and in the supracondylar region. Through an axillary laceration, the axillary artery could be seen pulsating. There was no radial or ulnar pulse, and the hand was cold. The brachial artery at the elbow was found to be so small that the surgeon did not at first believe it was the brachial artery. Periarterial stripping made no difference. The patient was transferred to another hospital, gangrene set in and amputation became necessary. Spasm or ligature of the brachial artery should not, by itself, cause gangrene. In the first World War, many other serious complications occurred, with only a small proportion of gangrene. Therefore, it is likely that the collateral circulation was equally involved in the spasm, and circulation was arrested throughout the distal arterial tree. Learmonth (82, 83) concluded that spasm may reduce blood flow by (1) affecting the collateral vessels, (2) reducing the caliber of the main vessel and (3) extending to the distal segments of the main artery. Recent investigations by Kinmonth, Simeone and Perlow (as yet unpublished, quoted by DeBakey and Amspacher) (84) indicate that at least in cats and rabbits arterial spasm can occur after trauma even in a sympathectomized or denervated limb. These investigations indicate that in its simplest form, traumatic segmental arterial spasm is a direct response of the blood vessel itself and is not mediated by reflexes.

Cohen (49) pointed out that none of the manifestations of traumatic

segmental arterial spasm show the commonly accepted behavior of reflex mechanisms. Although this may be true, there is an even larger body of evidence that indicates that arterial spasm in response to trauma must necessarily involve a nervous element (85, 86). Cohen (49), for instance, quoted a case reported by Bywater in which, after a crushing injury resulting from trapping of the right arm and right leg, the patient complained that the left arm had suddenly become numb and the pulse had disappeared from this limb. Shortly thereafter, the left leg suddenly became numb and the pulse there disappeared. The patient died, and at autopsy no arterial damage was found in any of the vessels of these limbs. Barnes and Trueta (87) have noted that after unilateral injury to the hind limb in rabbits, the arteries of the opposite limb will also be found to be in spasm. Shumacker (88, 89) has reported a series of cases in which arterial aneurysms have been associated with prolonged and intense vasospasm which disappeared after removal of the aneurysmal mass or following sympathectomy. He suggested that the aneurysm may serve as a constant focus of irritation, maintaining a state of spasm in the arterial tree.

The general experience in the treatment of arterial spasm indicates that sympathectomy may have a favorable influence, although this is not invariable and is in keeping with the fact that there must be a local spasm which is not of nervous origin. (90). Apparently other types of trauma may produce arterial spasm (91-94). Thus, a number of reports are found of arterial spasm in arteriosclerotic disease in which only localized occlusion or narrowing of the vessels occurs (95, 96). Leary and Allen (97) reported a number of cases of intermittent claudication as the result of arterial spasm induced by walking, and Pearl (98) reported 6 cases of angiospastic claudication in which the presence of an arterial lesion produced a hypersensitivity which resulted in vasospasm of the collateral vessels and the finer ramifications of the artery in the distal part of the body. Atlas (75) called attention to instances in which a minute embolus lodged in the periphery of the leg has given rise to bilateral spasm of such magnitude that an organic occlusion of the bifurcation of the abdominal aorta was simulated. Unless the possibility of spasm is considered in these circumstances, the larger spastic vessels may be explored surgically to remove what is erroneously considered to be the offending embolus. Gage and Ochsner (99) concluded that the sudden occlusion of any major peripheral artery produces the following pathologic-physiologic changes: (1) sudden obliteration of the peripheral pulse, (2) marked decrease in blood volume flow, (3) rapid fall in the temperature of the limb, (4) cessation of capillary pulsation, (5) marked and sustained decrease in arterial and venous pressures, and (6) moderate to severe vasospasm of the entire arterial tree distal to the arterial obliteration.

Morton and Scott (20) pointed out the similarity of this type of traumatic arterial spasm to that which is induced by repetitive trauma,

as by pneumatic hammer manipulation reported in the earlier section of the article, and indicated that they are but various degrees of the same general phenomenon. The condition is not only an acute one, but may become chronic. Gage (100) Morton and Scott (20) pointed out that some of the outstanding points to be noted in angiospasm following trauma are: (1) the hypersensitivity to cold, (2) the long duration of the vascular spasm after the acute effects of the trauma have subsided and the injured tissues have been repaired by scar, and (3) the fact that this predisposition to angiospasm may pass into a latent stage and remain dormant for a long interval, to be brought about again by certain conditions, particularly by cold. The frequency with which some degree of angiospasm follows many different types of trauma convinced these authors that an increased vasoconstrictor activity is the fundamental response to trauma and scar formation. It is probably true that a vasoconstrictor hypersensitivity is present in a latent form much longer and more commonly than is realized. Such a form often is not recognized, as it requires the proper physical conditions to make it apparent. The aching of scars on exposure to cold probably can be explained on this basis.

The participation of the sympathetic nervous system in the extension of spasm beyond the locus of direct injury is demonstrated by the work of Barnes and Trueta (87) who found that, following sympathectomy, the traumatic spasm did not affect the opposite limb, even though once spasm had set in, sympathectomy did not always remedy the situation. Supporting this study is the observation of Allen and Craig (101) that lesions of the nervous system may modify the circulation by the direct involvement of the vasomotor fibers. They reported the case of an individual who had a spinal cord tumor who had, in addition to somatic signs, cold and vasospastic extremities, which condition was relieved after the tumor was removed. There is a body of evidence to indicate that the peripheral vascular changes in cervical rib or scalenus anticus syndrome are equally due to interruption or stimulation of sympathetic vasomotor fibers, rather than to direct involvement of the artery in question (102, 103).

Apparently, the site of trauma need not necessarily be in the artery itself to produce vasospasm (99). Ochsner and DeBaKey have given evidence that in venous thrombo-embolic conditions, arterial spasm may exist on a reflex basis (105, 106). They collected a number of cases in which the localized venous thrombotic process apparently initiated marked vasospasm which involved both arterioles and veins. At times the vasospasm was so severe that the condition originally was considered to be caused by arterial embolism (107). In some cases gangrene developed. These authors demonstrated in animal experiments that localized chemical endophlebitis results in marked arteriolar spasm of severe degree in the limb peripheral to the thrombophlebitis (108). Apparently, as Leriche (109) has pointed out, removal of the

thrombus and ligation of the region involved often interrupts peripheral vascular spasm, presumably by preventing or stopping further afferent discharges that would otherwise maintain the spasm. The general concept gained from these reports is that occlusive phenomena and traumatic damage to arteries and veins produce difficulty in circulation not only by their direct occlusive action but also by causing, directly or reflexly, vasospasm in local and distant areas which adds to the difficulty produced by the occlusive or traumatic stimulus itself.

AXON REFLEX VASODILATATION

A final means of control of peripheral blood vessels is illustrated by two phenomena. First is the so-called triple response in which, following a local minor injury, a spreading redness extends around the region of trauma. Lewis (7-12) has demonstrated that this spreading redness is caused by local arteriolar vasodilatation which results from the operation of a local axon reflex. Anatomically, this reflex is based on the fact that afferent fibers have collateral fibers within the skin which pass to nearby blood vessels and there cause vasodilatation on a cholinergic basis. Lewis (7-12) has shown further that the same mechanism is involved in responses of the skin to prolonged cooling. It is known that if a hand is placed in cold water, the first response is vasoconstriction, but after a few minutes' immersion or even after removal of the hand, flushing begins and circulation increases to such a point that the hand becomes red. Apparently the prolonged stimulation of cold induces a minor type of local injury which, like mechanical trauma, initiates the axon reflex and dilates the arterioles. This mechanism is lost when the afferent fibers to the part degenerate, but it is maintained when the central connections to the fiber are cut off, and before degeneration occurs. A denervated area of skin, therefore, tends to become cooler and paler than normal skin after a period of flushing, owing to sympathetic release. It is possible that the axon reflex mechanism operates in normal circumstances to maintain a normal amount of local vasodilatation. It may well be that this is the function of the dorsal root "reflexes" reported by Toennies (110) who noted that, after stimulation of one afferent fiber, impulses could be seen emerging in the dorsal roots not only of that segment but also of adjacent segments on the same side, and on crossed dorsal roots in adjacent segments. Apparently these impulses pass antidromically outward to the skin and have no influence at the receptors, but by passing down axon collaterals they dilate blood vessels and maintain a normal blood flow to the skin. The interruption of these axon reflexes by skin denervation or by damage to the central terminals and to dorsal root ganglions, as in tabes, may well be responsible for the so-called trophic changes that occur under these circumstances.

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