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VASODILATING DRUGS ON THE CIRCULATION:
OBSERVATIONS ON VASOMOTOR GRADIENT**

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THE RESULT OF INTRA-ARTERIAL INJECTION OF VASODILATING DRUGS ON THE CIRCULATION: OBSERVATIONS ON VASOMOTOR GRADIENT

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The effect of vasodilating drugs is ordinarily short; such drugs frequently cannot be given orally, intravenously, or intramuscularly in amounts sufficient to effect marked vasodilatation because the general systemic effects are so great that administration of such amounts is inadvisable or prohibited. It was because of this consideration that the effects of injection of drugs directly into the arteries supplying the upper and lower extremities were studied. It is apparent that the concentration of a drug within the artery and its arterioles is much greater when the drug is injected directly into an artery than it is when the drug is injected into a vein or muscle, or taken by mouth. By the intra-arterial method of administration we hoped the drugs would be "fixed" in the extremity; this would allow the use of amounts which would produce marked vasodilatation in a single extremity without causing general systemic effects. Incidental observations lead us to a consideration of the difference of the ease with which vasodilatation can be induced in the upper and lower extremities.

METHOD OF OBSERVATION

In each instance the patient lay quietly in a room, the temperature and humidity of which were relatively constant for a few minutes before the observations were begun. Subsequent to injection the patient lay quietly until the observation was completed. In all instances the temperature of the skin was determined by the Sheard electric thermometer; a thermocouple was placed on a digit of each extremity. The skin overlying and the tissues surrounding the brachial and femoral arteries were infiltrated with a few cubic centimeters of a 2 per cent solution of procaine. The arteries were punctured with an ordinary venipuncture needle attached to a syringe containing 1 to 5 cc. of the solution of the drug to be injected. Papaverine hydrochloride in doses of 0.032 to 0.065 gram histamine phosphate in doses

of 0.1 to 0.15 mgm., and Acetyl B-methylcholine (mecholy) in doses of 0.5 to 2.0 mgm. were injected intra-arterially in the various cases. Only cases in which the temperatures of the digits were several degrees centigrade less than that attainable by vasodilatation were used in the final compilation, since it is apparent that when the temperature of the skin of a digit is high, which indicates marked vasodilatation, additional vasodilatation can be only minimal or cannot be induced.

The intra-arterial injection of papaverine hydrochloride

A solution of papaverine hydrochloride was injected into the brachial artery in ten cases. There was no detectable impairment of circulation to the upper extremities in any of these cases. There were four cases in which chronic occlusive arterial disease affected the lower extremities, and in the determination of averages shown in Figure 1, observation on the temperature of the toes in these cases was excluded. The remaining individuals were well or had hypertension or chronic arthritis. The usual local response was an immediate blush which involved the entire extremity distal from a level slightly above the site of injection. In a few minutes the temperature of the fingers supplied by the artery which was the site of the injection began to increase and a few minutes later the temperature of the digits of the opposite extremity began to increase. The temperature of the toes seldom increased and in several cases it actually decreased. While considerable variation in response of digital temperatures was noted in the various instances, the trend of change was almost uniform. The results of the ten observations are presented in the composite graph at the left of Figure 1. These observations seemed to indicate that the papaverine was "fixed" in the upper extremities, which were the site of the injection, since the average temperatures of the toes

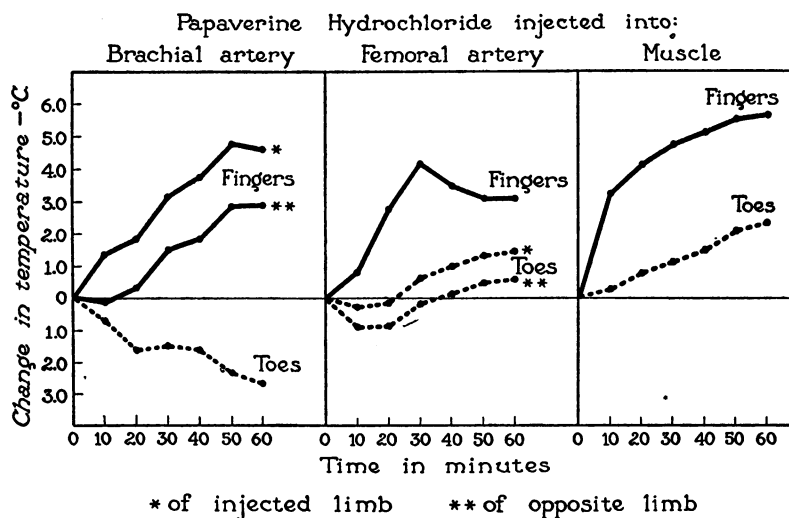


FIG. 1

The temperature of the toes decreased after injection of papaverine hydrochloride into brachial arteries while that of the fingers increased. However, injection into femoral arteries caused a smaller increase of temperature of the toes than of the fingers and produced effects similar in this regard to intramuscular injection of papaverine. The vasodilating effect of papaverine on the toes seems to be enhanced very little if at all on injecting it into the femoral artery.

did not increase. Subsequently, the drug was injected into the femoral artery in eight cases. Six of these were cases of chronic arthritis without hypertension or impairment of the circulation to the lower extremities, and two were cases of chronic occlusive arterial disease. Since the response of the temperature of the toes in these two instances was roughly the same as that of the toes in cases in which occlusive arterial disease was not present, the results are included in this study. The blush noted when the drug was injected into the brachial artery was usually entirely absent but occasionally occurred very faintly. Surprisingly, the average increase in temperature of the lower extremities was slight, while that in the fingers was much greater. While the response noted varied considerably in individual cases, the trend of change in temperature was roughly the same in each case. The results of the eight observations are shown in a composite graph in the central part of Figure 1. The results given for the fingers are in each instance the average of the increases in temperature of one finger on each hand.

The intramuscular injection of papaverine hydrochloride

Papaverine hydrochloride in doses varying from 0.097 to 0.2 gram was injected intramuscu-

larly in ten cases. Eight of the patients in these cases had Raynaud's disease, chronic arthritis, jaundice, or hypertension, without occlusive arterial disease, and two had occlusive arterial disease of the lower extremities. Since the changes in the temperature of the skin of the toes of patients who had occlusive arterial disease followed roughly the changes noted in the other observations, they are included in this report. The average response of the temperature of fingers and toes charted at the right of Figure 1 indicates a rapid and marked increase in the temperature of the fingers and a slower and less marked increase of the temperature of the skin of the feet. Subsequently, 0.097 gram of papaverine hydrochloride was injected intravenously. The temperature of the skin of the fingers increased 7.2° C. in fifty minutes while that of the toes decreased almost 1.0° C.

The intra-arterial injection of Acetyl B-methylcholine (mecholyll)

Acetyl B-methylcholine (mecholyll) was injected into the brachial arteries of four patients, three of whom had no occlusive arterial disease and one of whom had occlusive arterial disease in one leg, the digits of which were not used for the observation of the temperature. As in the ob-

servations on the effect of papaverine, immediately following the injection of mecholyl, an intense blush involved the entire arm distally from a level above the point of injection. The average temperature of the digits of the hand on the side of the injection increased in a few minutes, and the temperature of the digits continued to increase. The temperature of the fingers on the opposite hand likewise increased, but did so more irregularly and more slowly. The temperature of the toes increased to a much smaller degree. The results are shown in a composite graph in the left part of Figure 2. Mecholyl was then injected

cepted for final calculations. As in the observations with papaverine and mecholyl, an intense blush involved the skin supplied by the artery into which histamine had been injected, and the temperature of the extremity increased rapidly. The temperature of the digits of the opposite extremity increased slowly and less markedly, while that of the toes was influenced very little. The temperature of the fingers on the side of the injection increased an average of 5.0° C.; the temperature of the fingers of the opposite side increased 3.0° C., while the temperature of the toes decreased 0.4° C. in thirty minutes, but in the following twenty minutes it increased to 1.6° C. more than the temperature just before the injection.

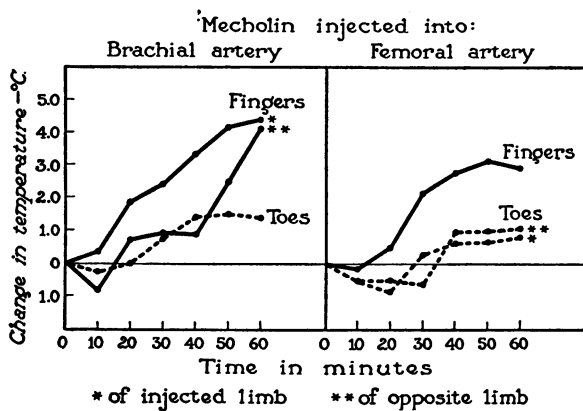


FIG. 2

Regardless of whether mecholyl is injected into brachial arteries or femoral arteries, vasodilatation is more marked in the fingers. The vasodilating property of mecholyl on any extremity is largely independent of whether it is injected into the artery supplying that extremity or into another artery.

into the femoral arteries of three patients, two of whom had arthritis. The results are shown in a composite graph at the right of Figure 2. As in the case of the intrabrachial injection of papaverine, the temperature of the skin of the fingers increased very much more than did that of the toes.

The intra-arterial injection of histamine

Histamine was injected into the brachial arteries of five patients. One of these patients had arthritis, one had multiple sclerosis, one had polycythemia, and two had thrombo-angiitis obliterans of the lower extremities. Only the temperature of the skin of the toes of the three cases in which occlusive vascular disease was absent was ac-

SUMMARY

The influence on temperature of the skin of digits of all extremities following the injection of histamine, papaverine, and mecholyl into the brachial artery and into the femoral artery are shown in Figure 3. It is apparent from these

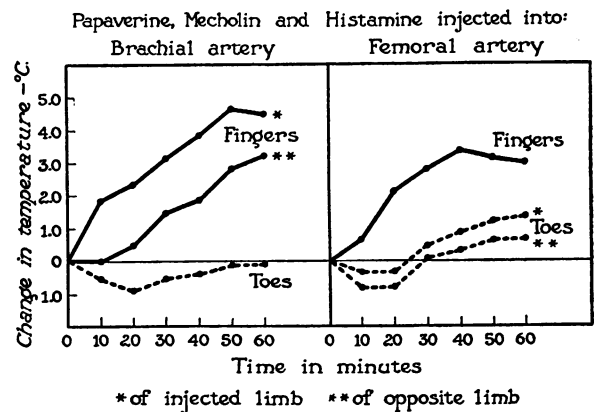


FIG. 3

The toes are relatively refractory to the vasodilating action of papaverine hydrochloride, mecholyl, and histamine, for increases in temperature of fingers are in composite significantly greater than those of toes, regardless of whether these drugs are injected into the brachial artery or the femoral artery.

observations that it is impossible to "fix" a vasodilating drug in an extremity to any great extent by injecting the drug into the artery supplying the digits. The effects on the temperature of the skin of the digits supplied by the artery into which the drug was injected and the effects on the

temperature of the skin of digits of other extremities were not much different from what they were when the drug was injected intramuscularly or into some other artery. For example, papaverine or mecholyl in the amounts which we have injected into a femoral artery have very little greater vasodilating effect on the digits of the lower extremity than when they are injected into the brachial artery, and the degree of vasodilatation in the hands is almost as great following injection into the femoral artery as that which follows injection into the brachial artery.

The relative refractoriness of arteries of the lower extremities to the effects of vasodilating drugs, however introduced into the body, is clearly indicated, for our composite graphs show that increases in temperature of the toes which indicate vasodilation either do not occur or are uniformly much less than those of the fingers (Figures 1, 2, and 3). This refractoriness to vasodilatation in the toes has been noted before by Pickering and Hess (2), who studied responses to warming of the body and found much earlier evidence of vasodilatation in the hands than in the feet, and by Horton, Roth, and Adson (1), who found that an increase in the temperature of the fingers occurred sooner and was much more marked than that of the toes when fever was induced artificially or when alcohol was ingested. This relative refractoriness to vasodilatation of the lower extremities seems to be a normal function of the human body. The explanation of it is not apparent, although it may be a part of the mechanism for the maintenance of blood pressure and circulation in the upright position which man maintains for much of his existence. Furthermore, this phenomenon appears to account, in some way not yet fully appreciated, for the predominance of occlusive arterial diseases in the lower extremities. Schmidt-Weyland (3) has shown that gangrene of a rabbit's ear can be produced by intravenous injection of bacteria provided 0.5 cc. of a 1:1,000 solution of epinephrine was injected daily near the base of the ear. The lesions so induced resembled those seen in thrombo-angiitis obliterans, and Schmidt-Weyland concluded that disturbance in circulation was necessary before bacteria or their toxins could produce vascular lesions. Perhaps this "disturbance" in circulation of man is the dominance of

vasoconstriction over vasodilatation in the lower extremities, as shown by the relative refractoriness to vasodilatation in this region. A definite solution to the high percentage of involvement of the lower extremities by the occlusive vascular diseases, arteriosclerosis obliterans, and thrombo-angiitis obliterans, cannot be given conclusively, but it appears to us to be based on some such peculiarity of circulation as we have emphasized in this presentation.

CONCLUSIONS

1. The vasodilating drugs, papaverine hydrochloride, Acetyl B-methylcholine (mecholyl), and histamine, cannot be "fixed" in an extremity to any great degree by injecting them into the lumina of arteries supplying the extremities. For example, the results on the temperature of the toes of the right foot of injecting mecholyl into the right femoral artery are about the same as those which follow the injection of mecholyl into the brachial artery.

2. The lower extremities contrasted to the upper extremities are relatively very refractory to vasodilating agents, as shown by the fact that the vasodilating drugs used produced moderate to marked increases in temperatures of the fingers and no increase or very little increase in the temperatures of the toes regardless of whether papaverine and mecholyl were injected into the femoral artery, into the brachial artery, or intravenously or intramuscularly. This refractoriness of vasodilatation in the lower extremities seems intimately associated in some way, as yet unexplained, with the much higher incidence of chronic occlusive arterial diseases in the lower extremities as contrasted with the incidence in the upper extremities.

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