Vasomotor Responses to Cooling in the Extremities of Subjects with Neurologic Lesions

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With the technical assistance of Gordon Gilbert, B.S., and Raleigh Wheeler, B.S.

Reflex vascular responses to cooling were studied in subjects with neurologic disorders, with a younger and an elderly "normal" group being used for comparison. By and large the responses were mirror images of those described for the Gibbon-Landis procedure. It was demonstrated that normal reflex responses to cooling as well as to warming are dependent upon the integrity of sympathetic innervation.

Evidence of vasoconstriction in remote skin areas in response to local application of cold has been reported by various investigators. Pickering studied this response thoroughly; he showed that immersion of one hand and forearm in cold water produced a transient vasoconstriction of the opposite hand.

Two modes of action are probably involved in the reflex vasoconstrictor response to cooling an extremity, one transient due to afferent nerve stimulation, and one lasting due to the cooling of a body of blood which reaches the vasomotor centers. This represents a Gibbon-Landis procedure with an opposite sign. The reflex vasoconstriction is considered a measure of conserving body heat.

Since the original work of Cannon and his co-workers, altered responses to vasodilator stimuli in sympathectomized limbs have been the subject of several independent studies. Lately, Redisch et al. were able to demonstrate that 7 of 11 sympathectomized lower limbs responded with a significant decrease in blood flow in response to a vasodilator stimulus (Gibbon-Landis procedure), while blood flow decreased as usual in the non-sympathectomized limb. Goetz also reported that, in some cases after sympathectomy, blood flow to the toe decreased in response to vasodilator stimuli. Prinzmetal and Wilson showed that blood flow in the upper extremity decreased in response to the Gibbon-Landis procedure after sympathectomy in 2 patients with Raynaud's phenomenon.

Information is less complete as far as vasoconstrictor stimuli are concerned. Barcroft and Dornhorst found a paradoxical response to cooling, namely, increase in blood flow in sympathectomized limbs. Ahmad reported a patient, unilaterally sympathectomized for hyperhidrosis, who showed vasodilatation in the unsympathectomized hand in response to cooling the sympathectomized side. So far, this has remained an isolated observation. Goetz reported an increase in pulse volume and rate of blood flow in completely sympathectomized lower extremities on cooling hands and forearm.

Hemiplegic limbs showed a delay of vasoconstrictor response to cooling, but no quantitative difference between the normal and hemiplegic sides. Uprus et al. stated further that, in general, the functional capacity of hemiplegic limbs for vasoconstriction in response to a sensory stimulus or fall in blood temperature is unimpaired. Sturup and co-workers arrived at the same conclusion and stressed that the reflex response to vasocon-
strictor stimuli is completely independent of the continuity of anterior and posterior nerve roots, as long as the sympathetic nerve fibers remain intact.

The effects of transection of the spinal cord upon blood flow and vasomotor responses seem to be entirely dependent upon the level and completeness of the lesion. These 2 factors influence directly the degree of interruption of sympathetic pathways. According to Pollock et al., injury to the spinal cord renders the affected limb more sensitive to a decrease in environmental temperature as indicated by surface temperature readings. They attributed this to failure of the excitatory neural impulses to stimulate body heat production, due to interruption of suprasegmental reflex activity. Gilliat et al. observed that in patients with cord lesions at T4 or lower, vasoconstrictor reactions in the fingers occurred in response to cold and other stimuli to head or neck. Bunke and Foerster were not able to elicit reflex vasoconstriction by stimulating cutaneous receptors below the level of the lesion. In case of midthoracic complete transection of the cord, they could produce vasoconstrictor responses in the arms by applying cutaneous stimuli well below the level of the lesion. Guttman and Whitteridge could not confirm Foerster’s observation: in their experiments, vasodilatation in response to visceral distention was mediated through fibers above the level of the lesion. The degree of disturbance in regulation of peripheral blood flow and other autonomous functions in complete spinal cord lesions increases in direct proportion to the height of the level of the lesion.

The following report deals with an attempt to determine more clearly the vascular reflex responses to cooling in subjects with neurologic lesions.

**Methods and Material**

All experiments were performed in a constant temperature room at 25 C. (+ 0.5°C) and 55 percent humidity; thus, a mild vasodilator stimulus was applied against which the presumably vasoconstrictor reflex response to cooling was tested. The subject was in “basal” state clad in cotton pajamas, with the extremities exposed, and was considered “adapted” when the surface temperature of the planar surface of the big toe had remained constant for at least 1/2 hour as recorded quasicon tinuously on a Speedo-max surface temperature recorder. One upper extremity was then immersed in a water bath maintained at 15 C. for a period of 40 minutes. Vasomotor responses in the lower extremity were ascertained by periodic determination of the rate of blood flow measured with a large limb venous occlusion plethysmograph. The following groups were compared: group 1, 5 young healthy adults; group 2, 6 elderly adults with demonstrable cardiovascular disease; group 3, 6 patients with peripheral occlusive arterial disease; group 4, 6 patients with hemiplegia; group 5, 7 patients with sympathetecmy; group 6, 4 patients with transection of the spinal cord.

**Results**

Basal flows in young normal subjects were higher than in elderly subjects without demonstrable cardiovascular or neurologic lesions; the blood flow changes in response to a vasoconstrictor stimulus (cooling) showed the following trend: Peripheral blood flow decreased by an average of 40 per cent compared to the basal flow, in both groups; the maximal vasoconstrictor response in the young normal adults was reached at about 25 minutes after the cooling procedure was started; in contrast, in the elderly adults without demonstrable vascular disease, the maximum response was reached only after an average of 45 minutes, that is, shortly after the discontinuation of the cooling procedure. Surface temperature was decreased in most but not in all cases parallel with the plethysmographically measured blood flow. The small number of patients in each group precludes statistical evaluation. It is for this reason that the results for each patient are given.

Hemiplegic limbs showed a somewhat lesser basal flow than those of elderly subjects of the comparative age group without demonstrable arterial occlusive disease. Blood flow in the hemiplegic limbs decreased regularly but only slightly in response to the vasoconstrictor stimulus (cooling); changes remained within the range of 2 ml./100 ml. tissue/min. Comparison of hemiplegic limbs with limbs of patients with documented oblitative ar-
TABLE 1.—Effects of Cooling Procedure on Blood Flow of the Lower Extremity
(ml./100 ml. tissue/min.)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Basal flow</th>
<th>Max. change</th>
<th>Time of max. response (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.A.</td>
<td>23</td>
<td>12.3</td>
<td>-4.0</td>
<td>32</td>
</tr>
<tr>
<td>P.H.</td>
<td>26</td>
<td>28.6</td>
<td>-10.3</td>
<td>36</td>
</tr>
<tr>
<td>P.J.</td>
<td>21</td>
<td>22.4</td>
<td>-6.6</td>
<td>29</td>
</tr>
<tr>
<td>M.M.</td>
<td>29</td>
<td>20.2</td>
<td>-6.0</td>
<td>29</td>
</tr>
<tr>
<td>R.P.</td>
<td>24</td>
<td>14.6</td>
<td>-4.3</td>
<td>29</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>19.6</td>
<td>-6.2</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 3 (hemiplegic patients)</th>
<th>Group 4 (elderly patients with obliterator vascular disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Age</td>
</tr>
<tr>
<td>---------</td>
<td>-----</td>
</tr>
<tr>
<td>W.E.*</td>
<td>63</td>
</tr>
<tr>
<td>P.E.*</td>
<td>49</td>
</tr>
<tr>
<td>H.C.</td>
<td>44</td>
</tr>
<tr>
<td>C.E.</td>
<td>60</td>
</tr>
<tr>
<td>M.R.*</td>
<td>58</td>
</tr>
<tr>
<td>F.M.*</td>
<td>45</td>
</tr>
<tr>
<td>Average</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patients with simultaneous obliterator arterial disease.
†Tested limb was previously sympathectomized.

TABLE 2.—Effects of Cooling Procedure on Blood Flow of the Lower Extremity (ml./100 ml. tissue/min.)*

<table>
<thead>
<tr>
<th>Sympathectomized limbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>P.M.</td>
</tr>
<tr>
<td>P.M.†</td>
</tr>
<tr>
<td>S.L.</td>
</tr>
<tr>
<td>K.W.</td>
</tr>
<tr>
<td>F.A.</td>
</tr>
<tr>
<td>D.J.</td>
</tr>
<tr>
<td>B.W.</td>
</tr>
<tr>
<td>Average</td>
</tr>
</tbody>
</table>

*Sympathectomy was performed because of obliterator arterial disease, except in P.M., who was operated on because of hypertension.
†Hemiplegic limb.

Hypertension (lumbodorsal resection) and 3 for obliterator arterial disease (lumbar resection). Average basal flows were higher in limbs sympathectomized for vascular disease than in the comparable nonsympathectomized arteriosclerotic group (table 1). There was an average increase of 44 per cent in blood flow in response to the vasoconstrictor stimulus in all subjects, except in 1 patient whose sympathectomized limb was paralyzed: he showed no change in blood flow. One patient who had been sympathectomized for obliterator arterial disease on one side had small decrease in flow in the nonsympathectomized limb similar to the response of patients with obliterator arteriosclerosis in general.

In the sympathectomized group (table 2), the maximal blood flow responses were reached at an average of 25 minutes after cooling was started. Again, correlation between surface temperature and measured blood flow was poor.17

In the 4 paraplegic patients, the average basal flow was somewhat higher than in the patients with obliterator arteriosclerosis, but...
lower than in the 2 normal control groups (1 and 2). Reflex responses to cooling differed with the site and extent of the lesions. The first of the 4 subjects studied (table 3) and diagnosed as having multiple sclerosis with spastic paraplegia showed a marked increase in blood flow in response to cooling without any change in surface temperature. The second case with a radiologically documented transection at C7-T1 showed a 3-fold increase in blood flow in response to cooling of one upper extremity. Transections of the cord at the levels T6-T8 and T11-T12, respectively, were present in the 2 patients who showed diminution of blood flow similar to the response of the elderly "normal" group.

A graphic comparison of responses to cooling in the various groups tested is shown in figure 1. The small number of subjects in each group does not permit statistical evaluation. Changes within each group were, however, invariably in the same direction.

**DISCUSSION**

Extremity blood flow in patients with various neurologic lesions and its behavior in the reflex response to a vasoconstrictor stimulus (cooling) reveal essentially "mirror images" of the vasomotor responses obtained by applying a vasodilator stimulus (warming). Lesions of the brain causing hemiplegia apparently do not interfere essentially with reflex responses to vasoconstrictor stimuli; it should be noted, though, that the decrease of blood flow in the hemiplegic limbs was smaller than in the comparable group of elderly subjects without neurologic or cardiovascular disorders. Three of the 6 hemiplegic patients have some degree of peripheral arterial occlusive disease, and their blood flows are therefore in general more nearly comparable to the group with obliterative vascular disease than those without it.

The results obtained in the surgically sympathectomized group (increase in blood flow) were rather expected, since a "paradoxical" pattern in the reflex response to warming (decrease in flow) had been observed previous-
COOLING AND NEUROLOGIC LESIONS

ly. The physiologic mechanism of such "reversal" of response to warming and cooling remains obscure and no satisfactory explanation can be offered so far. The same speculation as presented concerning reflex responses to warming may be mentioned here: sympathectomy possibly alters an enzymatic process in the vessel wall that is most probably responsible for vasomotor activity, namely, the catecholamine-amine oxidase reaction. It is unexplained why such alteration should become manifest only when a vasomotor stimulus (either vasodilator or vasoconstrictor) is applied. It may also be recalled again that Cannon and his co-workers have shown many years ago that denervation of an organ or part renders it more sensitive to epinephrine.

The reflex vasomotor responses to cooling in the paraplegic subjects were dependent on the level and completeness of their respective lesions similar to their previously reported reflex responses to warming. This corresponds to the accepted neurophysiologic concept, that sympathetic outflow to the lower extremities most probably starts at about the level of T₅-T₆. In keeping with that concept, 2 paraplegic patients with documented lesions at T₆-T₉ and T₁₁-T₁₂, respectively, displayed "normal" reflex responses to cooling: their blood flow decreased. The 3-fold increase in blood flow in response to cooling, that was encountered in the paraplegic patient with multiple sclerosis and therefore underdetermined locations of lesions, indicates, in all probability, an impairment of sympathetic pathways in the cord above T₅, since a subject with documented "high" transection exhibited the same response; blood flow in this limb increased almost 3-fold in response to cooling. It can be said that, by and large, patients with high transection of the cord (above T₅) behave in a manner quite similar to that of subjects after surgical sympathectomy.

SUMMARY

Reflex vascular responses to a physiologic vasoconstrictor stimulus (cooling of one upper extremity) were ascertained in young healthy adults, elderly patients without demonstrable cardiovascular disease, hemiplegic patients, paraplegic patients, and subjects after surgical sympathectomy. Both young and elderly "normals" responded to cooling with a decrease in blood flow (reflex vasoconstriction). Hemiplegic patients (with arteriosclerosis) showed but small decrease in blood flow response to cooling similar to a control group of patients with obliterative arteriosclerosis. Basal blood flow was higher in the sympathectomized limbs and all of these subjects except 1 had an increase rather than decrease in blood flow in response to cooling; 1 did not show any change; none had a decrease. Paraplegic patients responded differently depending upon site and extent of their lesions; the ones with high transection of the cord showed a response similar to those seen after sympathectomy, while low transection did not alter the vasoconstrictor response to cooling. By and large, reflex responses to cooling are a "mirror image" of the reflex response to warming. Normal responses in both instances seem dependent solely upon the integrity of sympathetic pathways.

SUMMARIO IN INTERLINGUA

Le reflexe responsas vascular a un physiologic stimulo vasoconstrictori (frigidation de un del extremitates superior) eseva determinate in juvene adultos de normal stato de sanitate, in patientes de etate avante sin demonstrabile morbo cardiovascular, in patientes hemiplegic, in patientes paraplegic, e in subjectos recentemente subjicite a sympathectomia chirurgic. Le subjectos normal—tant'juvene como etiam de etate plus avante—reageva al frigidation per un reduction del fluoxo de sanguine (i.e. per vasoconstriction reflex). Patientes hemiplegic con arteriosclerosis monstrava solmente un mie reuduction del fluoxo de sanguine in responsa al frigidation. In isto illes se comportava simile a un grupo de controlo de patientes con arteriosclerosis obliterative. Le fluoxo de sanguine basal eseva plus alte in extremitates sympathectomisate, e omne le subjectos in iste categoria—con 1 exception—manifestava un aug-
mento plus tosto que un reduction del fluxo de sanguine in responsa al fridigad. In le caso exceptional, null alteration eseva notate. Casos de reduction non occurreva del toto. Le patientes paraplegic reageva diversemente secundo le sito e le extension de lor lesiones. In casos de transsection alte del corda, le responsa eseva simile a illo vidite post sympathetomia, durante que transsection basse non alterava le responsa vasoconstrictori a fridigad. A generalmente parlar, le responsas reflexe a fridigad pare esser "imagines specular" del responsas reflexe a calefication. In ambe casos, le normalitate del responsas depende exclusivamente del integritate del vías sympathetic.

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Pre-Harveian Doubts of Galenic Doctrine

The basic problem of both Galen and Servetus was how to move the blood from the right ventricle of the heart to the left. Galen had declared that the blood sweated through minute openings in the septum of the heart although there was some passage by anastomosis between the minute branchings of veins and arteries. Servetus announced that the transit occurred by a long course through the lungs although a very little blood, as he said, may pass through the septum of the heart. We may then say that there were two possible routes for the blood and that by the closing of the one, the other became essential, and already Vesalius in 1543 had cast some doubts on the passage through the septum of the heart although his complete denial of this route does not appear until 1555. Nevertheless, the doubt is there from 1543, and either in relation directly to Vesalius or through the influence of his book there must have been discussion on this point among physicians although they were still too timid to express their anti-Galenical stand in the permanence of print. In essence, Servetus without doing violence to the anatomical facts of Galen, "the traditional authority," simply made what might be called a quantitative reversal in the functions of the parts involved by stating that the bulk of the blood passed through the lungs from the pulmonary artery into the pulmonary vein, of course, by anastomosis between the veins and arteries described by Galen, while a very little, as Servetus said, might pass through the septum of the heart. It seems quite possible that Servetus did not actually believe in the permeability of the septum, but Galenical tradition caused him to refrain from a clear denial.—Charles D. O'Malley. The Complementary Careers of Michael Servetus: Theologian and Physician. History of Medicine and Allied Sciences 8: 387, 1953.
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Circulation. 1959;19:583-589
doi: 10.1161/01.CIR.19.4.583

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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