Patterns of Surface Temperature Response to Various Agents

By Lothar Wertheimer, M.D., Walter Redisch, M.D., Kurt Hirschhorn, M.D., and J. Murray Steele, M.D.

Surface temperature response to 15 agents was studied at 20 C. and 55 per cent humidity. Toe temperature was considered representative of the body's "glomus area." Temperatures at forehead and cheek represented the "blush area." Diethylylmethanol, Hydergine, tetraethylammonium chloride, Priscoline, hexamethonium, Ildar and Dibenzyline produced a prompt rise in temperature in the glomus area without affecting the temperature in the blush area; nicotinic acid, Roniacol, histamine and papaverine caused the opposite response. Nitroglycerin had no effect on the temperature in the blush area; with the subject recumbent, it caused a fall in the glomus area. Hypertonic saline, aminophylline and Banthine had no effect on either glomus or blush areas.

During the course of studying effects of various "vasodilator" agents on surface temperature and peripheral blood flow, it appeared that the types of response elicited differed from one another. It was decided, therefore, to study systematically the vascular response to agents belonging to several distinct pharmacologic groups.

This report deals with response of surface temperature to various agents under controlled environmental conditions where the behavior of surface temperatures can be predicted with some accuracy. Since it was desired to test vasodilators, an environment calling forth a mild vasoconstrictor response was used, namely a temperature of 20 C. and humidity of 55 per cent. Under these circumstances, the following adjustments normally take place:

1. Within 30 to 60 minutes the temperature of the toes decreases until it approaches closely environmental temperature; it then remains relatively constant.

2. The temperature measured at the finger tips usually continues to fluctuate markedly, and its pattern of behavior varies from subject to subject.

3. The temperature of the rest of body surface (forehead, cheek, xiphoid process of sternum, thigh and leg) remains relatively constant throughout the experiments (34 to 35 C. on forehead and cheeks, and about 3 to 6 C. lower at test places over the rest of the body, roughly according to the downward gradient described in the literature).

The difference in behavior of the toes as compared with the fingers suggests that the lower extremities are concerned with the coarse basic adjustment to environment, while the upper extremities provide for the fine minute-to-minute regulation and response to such varying impulses as may arise from a full bladder, increased digestive or peristaltic activity, or mental and emotional stimuli.

The constancy of the temperatures of the forehead and cheek, which contain no glomus but possess the faculty of visible blushing, is in striking contrast to the variability of the temperature of the toes and fingers, which are known to be very rich in the neuromuscular-vascular thermostats called glomi. For the purpose of grouping the surface temperature responses to pharmacologic agents, the terms "glomus area" and "blush area" will be used in this paper. Since the fingers did not yield a constant baseline in response to the mild vasoconstrictor stimulus of 20 C., and since such...

From the Research Service (Third New York University Medical Division), Goldwater Memorial Hospital, and the Department of Medicine, New York University College of Medicine, New York, N. Y.

This work was supported in part by the National Heart Institute, National Institutes of Health, and in part by the Public Health Research Institute of the City of New York and the Josiah Macy, Jr. Foundation.
baseline appears essential for measuring responses to a vasodilator stimulus the toes were chosen as representative of the “glomus area”; forehead and cheek were used as representative of the “blush area.”

**METHOD AND MATERIAL**

The subject, under basal conditions, was placed in the constant-temperature room maintained at 20°C and 55 per cent humidity. Surface temperature was recorded on a Speedomax from both great toes, the forehead and the cheek. The drugs were not administered until temperatures had remained constant for at least 30 minutes.

The response to 15 agents was tested in 74 experiments. Fourteen of these agents were administered in single doses: one of them was given in intravenous infusion, one sublingually, one by intramuscular route and 11 by intravenous injection. The fifteenth agent was fed orally over a four-week period and experiments were repeated at regular intervals in a manner previously described.

**RESULTS**

Seven of the drugs used had a marked dilator effect upon the glomus area and did not affect the blush area (fig. 1). These drugs included: diethyleno alcohol, three blockers of sympathetic pathways (tetraethylammonium chloride, Priscoline and hexamethonium), an agent known to depress central vasomotor tone (Hydrgine), and two so-called adrenergic blockers (Dibenzyline and Ilidar) known to interfere with the activity of circulating

**TABLE 1.—Surface Temperature Responses to Fifteen Agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Physiologic-Pharmacologic Classification of Agent</th>
<th>Dose Employed</th>
<th>No. of Subjects</th>
<th>Av. Change in Glomus Area (baseline temp. 20-21°C)</th>
<th>Average Change in Blush Area (baseline temp. 34-35°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td>&quot;Coronary&quot; vasodilator and &quot;peripheral&quot; vasodilator</td>
<td>0.6 mg. sublingually recumbent 7</td>
<td>-1.8 C. 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5% Saline</td>
<td>Hypertonic solution</td>
<td>250 ml. i.v. 4</td>
<td>0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminophylline</td>
<td>Bronchodilator, diuretic</td>
<td>225 mg. i.v. 4</td>
<td>0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Banthine</td>
<td>Cholinergic blocker</td>
<td>50 mg. i.m. 2</td>
<td>0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papaverine</td>
<td>Antispasmodic alkaloid</td>
<td>100 mg. i.v. 2</td>
<td>0 +1.3 C.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histamine</td>
<td>Capillary vasodilator</td>
<td>0.025 mg. i.v. 2</td>
<td>0 +1 C.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>&quot;Peripheral&quot; vasodilator</td>
<td>100 mg. i.v. 5</td>
<td>0 +2.4 C.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roniacol</td>
<td>&quot;Peripheral&quot; vasodilator</td>
<td>100 mg. i.v. 8</td>
<td>0 +1.8 C.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diethylaminoethanol</td>
<td>Vasodilating component of procaine</td>
<td>4.3 Gm. i.v. 7</td>
<td>+4.1 C. 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrgine</td>
<td>Central vasomotor depressor</td>
<td>0.3 mg. i.v. 3</td>
<td>+5.0 C. 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetraethylammonium</td>
<td>Sympathetic ganglionic blocker</td>
<td>300 mg. i.v. 3</td>
<td>+4.0 C. 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>chloride</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Priscoline</td>
<td>Sympatholytic</td>
<td>50 mg. i.v. 4</td>
<td>+4.5 C. 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hexamethonium</td>
<td>Sympathetic and parasympathetic ganglionic blocker</td>
<td>10 mg. i.v. 4</td>
<td>+5.6 C. 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ilidar</td>
<td>Adrenergic blocker</td>
<td>3 mg. i.v. 3</td>
<td>+4.7 C. 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dibenzyline</td>
<td>Adrenergic blocker</td>
<td>120 mg. orally O.D. for 5 weeks 13</td>
<td>+4.5 C. 0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 1.** Simplified reproduction of quasicontinuous Speedomax curves exemplifying response in glomus areas.
sympathomimetic amines\textsuperscript{11,16} (table 1). All of these agents in acute experiments produced a prompt rise in the temperature of the toes. Their effect was about equal in degree (toe temperature rose from about 20°C to between 24 and 25°C), and it invariably outlasted the experiment (about 45 to 60 minutes after onset of response). These facts suggest that the action of the drugs in this group is probably mediated by a rather sudden decrease of sympathetic vasomotor tone. The mode of action of diethylaminoethanol is entirely unknown, but, since its effect on surface temperature so closely resembles that of the six other drugs, all of which are known to affect sympathetic vasomotor tone in one way or the other, the inclusion of alcohol in this group seems justified.

Four of the agents tested have regularly increased the temperature in the blush area, and not in the glomus area (fig. 2). The resulting rise in temperature in the blush area was as prompt as that described in glomus area, but the rise was smaller (from about 35°C to about 37°C) and of much shorter duration (15 minutes in the average). (See table 1.) Nicotinic acid and Roniacol are closely related chemically but have no chemical or pharmacologic relationship to histamine and papaverine.

Vasodilator action produced upon surface vessels by the four agents in the blush area is confined to the minute circulation since there are no glomi in this area. Their mode of action is unknown. It has been suggested\textsuperscript{17} that cholinergic sympathetic fibers might be dominant in maintaining vasomotor tone in the blush area of the face in contrast to other surface areas where adrenergic fibers are assumed to be the main pathways of vasoconstrictor impulses.\textsuperscript{18} In order to obtain some information concerning this question, Banthine\textsuperscript{19} was injected intramuscularly in doses of 50 mg. It produced regularly the signs of cholinergic blockade, especially marked dryness of the mouth and transient disturbance in visual accommodation, but no measurable effect on surface temperature (table 1). Thus, while blocking of adrenergic sympathetic innervation in various ways regularly increased the toe temperature and never affected the temperature of the blush area, cholinergic blockade produced no effect in either of the tested areas.

Hypertonic saline and aminophylline likewise had no measurable effect on surface temperature in either blush or glomus areas (table 1).

Nitroglycerin was given in both the erect and the recumbent positions since it had been found\textsuperscript{20,21} that administration of nitroglycerin with the subject in the erect position may induce circulatory collapse by postarteriolar dilatation, venous pooling and reflex arteriolar constriction but that its administration with the subject in the recumbent position will not produce this response. There was a slight decrease in toe temperature following nitroglycerin when the subject remained recumbent; no measurable change occurred in either test area when the subject was tilted into a semi-erect position to an angle of 65 degrees and the drug was then administered (table 1). It should be noted that tilting from the recumbent to the erect position, per se, produced a decrease in toe temperature comparable to that produced by nitroglycerin when administered to the recumbent subject.

**DISCUSSION**

It has been shown\textsuperscript{22} that one and the same vasomotor agent or procedure may produce vasodilatation in one vascular bed and simultaneously vasoconstriction in another. The data presented here indicate that even within one vascular bed (in this case that of the skin)
areas can be differentiated by specific patterns of vasomotor response. Thus, although various drugs may be grouped together under the general designation vasodilator or vasoconstrictor, their individual effects may vary widely according to the location, extent and mechanism of action. Detailed information concerning the action of each drug thus adds to the knowledge of the physiologic behavior of the vascular system. Likewise, such information is obviously essential for choosing the most suitable drug for a particular therapeutic purpose.

**Summary and Conclusions**

1. Surface temperature response of normal subjects to 15 agents reported to have vasodilator action was tested in an environment of 20 °C and 55 per cent humidity (mild vasoconstrictor stimulus).

2. Four agents tested regularly caused a temperature rise in the blushing area and none in the glomus area, and seven produced a marked temperature rise in the glomus area but not in the blushed area. Four agents produced no increase of skin temperature in either of the test areas.

3. The seven agents which affected the temperature of the glomus area all act by interfering with the transmission of adrenergic impulses at various levels of sympathetic vasomotor pathways.

4. Interference with the transmission of postganglionic cholinergic impulses (by the administration of Bantthine) did not result in any measurable temperature changes in the areas tested.

**Summario in Interlingua**

15 agentes con un reputacion de virtute vasodilatative esseva studiate in lor effectos super le temperatura superficial. Le genas e le fronte esseva usate como representantes del areas erubescente, le digitos del pede como representantes del areas glomeral. In un ambiente de calor moderate (20°C con 55 pro cento de humiditate) le sequente resultatos esseva obtene: Papaverina, histamina, acido nicotinic, e Roniacol resultava invariavelmente in augmentos de temperatura del areas erubescente sed nunquam del areas glomeral. Per contrasto, diethylaminoethanol, Hydergina, clorido de tetraethylammonio, Priscolin, hexamethonium, Ilidar, e Dibenzyline augmentava invariavelmente le temperatura del areas glomeral sed non afficeva le temperatura del areas erubescente.

Blocages cholinergic per medio de Bantthine, aminophyllina, e solution salin hypertonic non resultava in ulle effecto super le temperatura del pelle. Nitroglycerina produceva un abassamento del temperatura in le areas glomeral quando le subjecto se trovava in un position recumbente.

**References**


4 —, —, and —: Physiological reactions of the human body to various atmospheric humidities. Am. J. Physiol. 120: 298, 1937.


13 Ahlquist, R. P., Huggins, R. A., and Woodbury,
SURFACE TEMPERATURE RESPONSE TO VARIOUS AGENTS


Moore, P. E., Richardson, A. W., and Green, H. D.: Effects of a new dibenzazepine derivative, RO2-3248, 6-allyl-6,7-dihydro-5H-dibenz(e,e)azepine phosphate (Ilidar) upon the blood flow, the peripheral resistance and the response to injections of epinephrine of the innervated hind limb of a dog. J. Pharmacol. & Exper. Therap. 106: 14, 1952.


