The sympathetic release test: a test used to assess thermoregulation and autonomic control of blood flow

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The sympathetic release test: a test used to assess thermoregulation and autonomic control of blood flow. Adv Physiol Educ 38: 87–92, 2014; doi:10.1152/advan.00095.2013.—When a subject is heated, the stimulation of temperature-sensitive nerve endings in the skin, and the raising of the central body temperature, results in the reflex release of sympathetic vasoconstrictor tone in the skin of the extremities, causing a measurable temperature increase at the site of release. In the sympathetic release test, the subject is gently heated by placing the feet and calves in a commercially available foot warming pouch or immersing the feet and calves in warm water and wrapping the subject in blankets. Skin blood flow is estimated from measurements of skin temperature in the fingers. Normally skin temperature of the fingers is 65–75°F in cool conditions (environmental temperature: 59–68°F) and rises to 85–95°F during body heating. Deviations in this pattern may mean that there is abnormal sympathetic vasoconstrictor control of skin blood flow. Abnormal skin blood flow can substantially impair an individual’s ability to thermoregulate and has important clinical implications. During whole body heating, the skin temperature from three different skin sites is monitored and oral temperature is monitored as an index of core temperature. Students determine the fingertip temperature at different skin sites is monitored and oral temperature and is monitored as an index of core temperature. Students determine the fingertip temperature at which the reflex release of sympathetic activity occurs and its maximal attainment, which reflects the vasodilating capacity of this cutaneous vascular bed. Students should interpret typical sample data for certain clinical conditions (Raynaud’s disease, peripheral vascular disease, and post-sympathectomy) and explain why there may be altered skin blood flow in these disorders.

heat stress; skin temperature; skin blood flow; sympathetic vasoconstrictor nerves

In this practical activity, we use thermal stimulation as a noninvasive physiological test to measure sympathetic vasoconstrictor activity in healthy subjects. The vasodilating capacity of an extremity with heating is measured through changes in skin temperature at that site and in the finger reflects the release of sympathetic vasoconstrictor tone. During the activity, students monitor skin temperature and oral temperature and graph their results. The normal response is attenuated in certain clinical disorders. Students should be able to predict the value of the sympathetic release test in the clinical assessment of patients with cold extremities, peripheral vascular disease, and post-sympathectomy.

Background

Core body temperature is controlled within a very narrow range, and thermoregulatory control of skin blood flow is critical to body temperature homeostasis during thermal challenges. Cutaneous and tissue blood flow can vary widely depending on the environmental temperature, for example, during cold exposure, hand blood flow can be as low as 0.15 ml·100 ml⁻¹·min⁻¹, lower than the metabolic requirements of the tissue, and can increase ~200-fold during heat stress (21). The temperature of the fingers depends on the rate of blood flow through them and the metabolism of the tissues. In skin, metabolism is so low that it can be ignored for practical purposes so that finger skin temperature directly correlates with skin blood flow (1, 2, 15).

An increase in skin blood flow reflects heat carriage away from the core and to the body surface, where its subsequent dissipation facilitates cooling of the core. Normal autonomic function is critical in controlling skin blood flow (4). There are two types of sympathetic nerves involved: noradrenergic vasoconstrictor nerves and cholinergic vasodilator nerves. Both are involved in temperature regulation. Hair-bearing skin (non-glabrous skin) is innervated by sympathetic vasoconstrictor (responsible for passive vasodilatation) and vasodilator (responsible for active vasodilatation) nerves. In this skin type, cutaneous blood flow is primarily increased by active vasodilatation, although a small initial increase in blood flow is due to the release of vasoconstrictor tone (7).

Nonhair-bearing skin (glabrous skin), which is present on the palms (including the fingertips), soles, and lips, is innervated solely by vasoconstrictor nerve fibers. An increase in blood flow in glabrous skin is therefore entirely achieved through the release of vasoconstrictor tone (8, 10). Glabrous areas have numerous arteriovenous anastomosis located in the lower dermis, which are richly innervated by sympathetic vasoconstrictor nerves. Large changes in skin blood flow can come about through the opening and closing of arteriovenous anastomosis. Sympathetic vasoconstrictor nerves to the skin are minimally tonically active in humans in thermoneutral environments. In moderately cool conditions, however, sympathetic vasoconstrictor fibers are active, and withdrawal of this activity can lead to an increase in skin blood flow of ~20% (16). Figure 1 shows an overview of autonomic control of peripheral blood flow to glabrous skin.

When core temperature is normal and skin temperature is increased, it has been shown that reflex effects of raising whole body skin temperature on skin blood flow are mediated through sympathetic vasoconstrictor withdrawal (16). However, if core temperature is increased with body heating, it can reach a threshold value at which the cutaneous active vasodilator system becomes fully active and sweating will also begin (12). Basal skin temperature should be considered before body heating. It has been determined that starting with a high skin temperature may lead to early activation of the sympathetic vasodilator system and affect an individual’s ability to separate...
Learning Objectives

After completing this activity, the student will be able to:
1. Describe the role of sympathetic vasoconstrictor nerves in the regulation of skin blood flow.
2. Recognize the contribution of the cutaneous circulation to thermoregulation.
3. Collect and analyze data and draw appropriate conclusions.
4. Represent the data in an appropriate form.
5. Investigate clinical scenarios where the sympathetic release test could be useful in assessing disorders of blood flow.
6. Interpret test results that are typical of patients with Raynaud’s disease, peripheral vascular disease, and postsympathectomy.

Activity Level

This activity is suitable for students studying a variety of courses, including physiology, anatomy and physiology, human biology, biomedical science, medicine, nursing, and the allied health sciences. Currently, we perform this activity with our first-year medical students.

Prerequisite Student Knowledge

Before doing this activity, students should have a basic understanding of:
1. Thermoregulation.
2. Sympathetic nervous system control of blood vessel diameter.

Time Required

A 15-min period should be allowed for the stabilization of baseline temperature readings. The subject is heated for ~20–45 min, during which time release of basal sympathetic tone should occur. The subject is then observed for 15 min after the release of sympathetic tone. If there is a subject who suffers from Raynaud’s disease, this time period would be protracted. Twenty minutes should be sufficient for the plotting of the gathered data. Students may be given 20–30 min to discuss why this test might be informative in the assessment of various clinical disorders. Students can be shown sample data for patients with Raynaud’s disease, peripheral vascular disease, and postsympathectomy and given an opportunity to interpret what they see. The overall duration of this activity is 2–3 h.

METHODS

Equipment and Supplies

The following equipment and supplies are needed for this activity:
1. Temperature-measuring devices [core temperature: oral thermometer or tympanic thermometer; skin temperature: hand-held devices are most practical (thermocouple thermometer, thermister thermometer, or infrared thermometer); room temperature: room thermometer].
2. Any commercially available foot warmer (we use a Beurer model) that reaches a temperature of ~115°F or, alternatively, a basin of warm water at a temperature of 115°F.

Optional. The following equipment and supplies are optional:
1. Cobalt blue paper (which turns from blue to pink when it comes in contact with sweat on the skin).
2. A heart rate monitor.
3. Laser-Doppler flowmetry or venous occlusion plethysmography (to measure finger skin blood flow).
**Human Subjects Approval**

This noninvasive experiment does not require ethical approval at Queen’s University Belfast. Adopters of this activity are responsible for obtaining permission for human research from their home institution. For a summary of the American Physiological Society’s “Guiding Principles for Research Involving Animals and Human Beings,” please see [www.the-aps.org/mm/Publications/Ethical-Policies/Animal-and-Human-Research](http://www.the-aps.org/mm/Publications/Ethical-Policies/Animal-and-Human-Research).

**Instructions**

The subject should initially be lightly clad to ensure a high degree of sympathetic tone at a room temperature between 59 and 68°F. Normally, skin temperature of the fingers is 65–75°F in these conditions and rises to 85–95°F during body heating when the fingertip temperature plateaus.

Subjects remain seated throughout the experiment with the dorsal side of one hand exposed (temperature measurements will be made from this hand throughout the experiment). Control observations are made for 15 min or longer if necessary.

At the end of the control period, body heating begins. The subject’s feet are placed into the foot warmer/hot water (maintained at 115°F or as hot as can be comfortably borne by the feet) and the body is draped with blankets, well tucked in at the back and sides. Only the forehead and hands are exposed.

Some duties are allocated to observers, as follows:

1. Measure the oral/aural temperature every 3 min (measured as an index of internal temperature). The site of core temperature measurement is important in terms of the validity and reproducibility of the measurement. If oral or aural temperature measurements are used in this experiment, be consistent and do not vary between the two. Be aware that body temperature measurements at different sites can be influenced by factors that specifically relate to that site, for example, factors that influence oral temperature measurements include heavy breathing, mastication, smoking, and previous consumption of hot or cold substances. For a scholarly review of this area, please see Ref. 19.
2. Record the room temperature every 3 min.
3. Apply the hand-held thermometer lightly and in rotation to the following sites:
   1. The pulp of the middle finger of one hand (the pulp is the padded area of the fingertip).
   2. A point (marked by an ink cross) on the back of one hand.
   3. A point (marked by an ink cross) on the forehead.

Relative, not absolute, changes in temperature are important. The areas where measurements are made are not covered so that responses to whole body increases in skin temperature are solely due to reflex responses and not due to local effects of temperature on blood flow.

At each place, contact is maintained until the temperature reading is steady.

The pulse at one wrist may be counted for 30 s each minute every 3 min and reported as heart rate (in beats/min). Watch for sweating on the face and hands (use cobalt blue paper if available) and report its first appearance.

**Trouble Shooting**

In our laboratory, we found that it can take up to 45 min in some normal individuals for sympathetic tone to be released.

Our anecdotal evidence shows delayed responses to heating in individuals of Asian ethnicity. Perhaps this is not surprising since it is well known that there are differences in vascular reactivity to sympathetic stimulation in black and white normotensive individuals. Certain drugs may also confound the normal response profile, for example, pseudoephedrine found in over-the-counter decongestant remedies is a peripheral vasoconstrictor, as are β-blockers. Students who have been prescribed these drugs should not volunteer as subjects. Individuals who have smoked or consumed caffeine on the day of the experiment should also be excluded as subjects.

**Safety Considerations**

Individuals with any of the following conditions should NOT serve as a subject:

1. Colds.
2. Chest complaints.
3. Heart conditions.

A review of the literature shows that normal oral temperature varies by 10.2°F (18) however, this activity should be stopped if oral temperature rises to 100°F (fever) or the subject feels faint.

**RESULTS AND DISCUSSION**

**Expected Results**

Expected results are shown in Figs. 2 and 3.

**Evaluation of Student Work**

Students should present their data graphically. Temperature should be plotted against time. Heart rate data may be included on a separate axis on the same graph.

Students should pool their data and identify any trends. Statistical analysis can be performed via ANOVA.

**Questions**

1. Why is finger skin temperature used as a measure of finger blood flow in this experiment?
ANSWER. The temperature of the fingers depends on the rate of blood flow through them and the metabolism of the tissues. In skin, metabolism is very low and can be ignored for practical purposes, so that finger skin temperature directly correlates with skin blood flow. Finger skin temperature is used to assess the extent of sympathetic tone release since it alone is innervated solely by sympathetic vasoconstrictor nerves. An increase in blood flow to the other sites (hand and forehead) may be due to active vasodilation as a result of the activation of cholinergic sympathetic fibers, although sweating should be visible on the forehead if this occurs and body heating should be stopped.

Question 2. Describe the process of thermoregulation in this experiment with reference to the release of basal smooth muscle tone in cutaneous blood vessels.

ANSWER. The hypothalamus is the integration center for thermoregulation. It receives afferent signals from thermal receptors in the skin. There are warm skin receptors as well as cold skin receptors. Although these warm skin receptors are not as important as the central warm receptors (in the hypothalamus and spine) in terms of overall body thermostasis, these receptors act as an early warning system for the body. The anterior hypothalamus is the heat loss center and is responsible for the reflex release of vasoconstrictor tone seen in this experiment.
Question 3. Patients with Raynaud’s disease often have digits that, when exposed to cold, become pale or perhaps purple. Explain these symptoms in terms of sympathetic vasoconstrictor nerve activity.

ANSWER. Vasospasm is typical of Raynaud’s disease and is as a result of hyperactivity of the sympathetic vasoconstrictor nerves, particularly to the digits of the hands and feet. This means that vascular resistance is high and blood flow is reduced, as is evidenced by whitening (blanching) of the fingers and ischemic pain. As blood flow is reduced, finger temperature falls. Reddening of the fingers on warming is more than likely reactive hyperemia. The purple appearance of digits in the cold indicates cyanosis.

Question 4. Can you suggest a possible therapy for Raynaud’s disease?

ANSWER. Some patients benefit from sympathectomy, which means that there is surgical interruption of the sympathetic nerves to the affected region. Sympathectomy may be beneficial to individuals who show poor increases in skin blood flow during heating and often abolishes symptoms. Sympathetic inhibition increases flow considerably, and, under normothermic conditions, resting finger blood flow is increased postsympathectomy compared with the control. The high skin temperature (caused by the increased blood flow) indicates successful outcome to the sympathectomy. Postsympathectomy there is no increase in finger blood flow during body heating; it is maximal in the thermoneutral environment. Sympathectomy is controversial and is reserved for patients unresponsive to all other measures. Clinical studies have shown that this benefit is not always permanent, however, and symptoms may return over time. Pharmacological treatment of Raynaud’s disease may involve Ca$^{2+}$ channel blockers, which relax smooth muscle, thereby dilating small blood vessels, $\alpha$-blockers, which counteract the effects of norepinephrine, and/or various vasodilators, such as nitroglycerine topical cream.

Raynaud’s Disease. There is hyperactivity of sympathetic vasoconstrictor nerves in response to cold or emotion. At a room temperature of 59–68°F, the patient has a skin temperature that is just above room temperature (i.e., the extremities are cold), while the control subject’s finger can be up to 40°F warmer (a normal level of sympathetic vasoconstriction). In response to body heating, skin temperature increases in both the control and patient, reaching a similar maximum plateau level in both, reflecting a comparative vasodilator capacity, however, the patient with Raynaud’s disease takes longer than normal to warm on heating. When body heating stops, sympathetic vasoconstriction increases again and blood flow falls.

Peripheral vascular disease. At a room temperature of 59–68°F, the patient has a skin temperature that is just above room temperature, while the control subject’s finger can be up to 40°F warmer. If the artery is very occluded, then blood flow cannot increase very much at all (as shown in Fig. 3), but if the artery is only very partially occluded, a reduction in the peak skin temperature would be expected compared with normal and the digits remain cold.

Question 5. Using the sample trace for finger skin temperature (shown in Fig. 3), compare the finger skin temperature response to body warming in four subjects and suggest a possible explanation for the findings on the basis of sympathetic control of cutaneous blood flow.

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Question 6. How do you think a diabetic patient would respond to body heating?

ANSWER. Students may talk about the complications associated with diabetes. Skin blood flow is actually increased in diabetes mellitus. The mechanism is not well understood and appears to be multifactorial. It is known that diabetes mellitus is accompanied by autonomic dysfunction. A loss of sympathetic control to arteriovenous anastomosis and precapillary sphincters (17) has been postulated. This could lead to shunting, which would result in the capillaries of the skin being bypassed and nutritionally deficient, which can cause ulcers. Capillaries can also become occluded (14), and, therefore, over time, the skin loses its ability to dilate and there is an attenuated blood flow increase in response to body heating.

Question 7. Why do you think this test is known as the sympathetic release or withdrawal test?

ANSWER. In response to heat stress, the anterior hypothalamus inhibits sympathetic vasoconstrictor fiber activity. Blood vessels are effectively released from normal sympathetic vasoconstrictor tone and, hence, the term “sympathetic release test.”

Inquiry Applications

Further exploration of the themes developed in this practical can be encouraged by asking students the following questions:

- Why might different people have different threshold temperatures for the release of sympathetic vasoconstrictor tone? You may want to discuss varying responses in populations of different weights, ages, races, or sexes.
- Why does heart rate increase with body heating? This probably relates to temperature effects on pacemaker activity at the sinoatrial node as well as autonomic influences.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


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