Sudomotor function in human poikilothermia

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Article abstract—Hypohidrosis predisposes to hyperthermia and may indicate generalized thermoregulatory failure. To assess the sweating capacity in human poikilothermia, we performed a quantitative analysis of the central and peripheral sudomotor pathways in four women with acquired poikilothermia (aged 29 to 38 years) and nine controls. Heat challenge in a climatic chamber (ambient temperature 40 °C, 50% relative humidity) for 180 minutes revealed that both sweat secretion and evaporative weight loss were significantly lower in the patients than in the controls (p < 0.01). Temperature thresholds for thermal sweating were markedly elevated in at least two patients, whereas a third patient showed no sweating response. Stimulation of the eccrine sweat glands by intradermally injected acetylcholine during reduced core temperature (34.9 ± 0.7 °C) revealed a significantly reduced sweating response in all patients (p < 0.01); the sudomotor response to pilocarpine iontophoresis was reduced or absent in three patients. We conclude that the generalized thermoregulatory sudomotor failure in these patients was attributable primarily to disorders of the central sudomotor drive; the impaired postganglionic sudomotor response is temperature related and possibly secondary to (long-standing) poikilothermia. Quantification of heat-dissipating capacity is pivotal for diagnosing severe thermolability and may help to prevent serious heat illness.

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Human thermoregulation is achieved by a complex interaction of autonomic, endocrine, and behavioral responses; the skin plays an important role in both afferent and efferent thermoregulatory pathways. Humans have a limited physiologic capacity to withstand cold stress but can dissipate heat most effectively, principally by sweating and peripheral vasodilatation. If ambient temperature exceeds body surface temperature, the only mechanism to maintain thermal equilibrium is evaporative heat loss; evaporation of 1 liter of sweat can remove 2,450 kJ (585 kcal).

The control of thermal sweating is influenced by information from central and peripheral thermoreceptors and is coordinated predominantly by the preoptic area/anterior hypothalamus; the efferent sympathetic sudomotor function is mediated by both preganglionic centers and postganglionic cholinergic pathways.

Poikilothermia, defined as fluctuation in core temperature of more than 2 °C due to changes in the ambient temperature, is the most common disorder of thermoregulation in humans and is usually caused by lesions of the posterior hypothalamus or brain stem, but its pathophysiology remains largely unknown. The disorders of heat production and heat conservation in poikilothermic patients predispose to marked hypothermia. However, if the preoptic region or peripheral heat-dissipating pathways are also affected, the patients are susceptible to severe hyperthermia, including heat stroke, particularly in combination with inadequate behavioral thermoregulation and possible use of drugs that suppress sudomotor function. Decreased sweat secretion during supranormal core temperature has been reported in some patients with poikilothermia; however, the sudomotor capacity in poikilothermia has not yet been quantified.

We investigated the heat-dissipating mechanisms in four patients with acquired poikilothermia, most probably of hypothalamic origin. We have previously demonstrated that our patients meet the definition of poikilothermia. We recently reported on the thermoregulatory responses to cold and heat challenge in our patients including some data on thermal sweating that are also described in the present study.

The rationale for the current study was to investigate the functional integrity of the central and peripheral sudomotor pathways by quantitative assessment of thermoregulatory sweating and postganglionic sudomotor responses in our patients.
Methods. Subjects. We investigated four women (aged 29 to 38 years) with acquired poikilothermia. All patients had a normal history of thermal sweating previous to the occurrence of poikilothermia but reported absence of sweating since then.

Patient 1 was a 29-year-old woman who was treated in 1983 by surgery and radiation therapy for a large tumor near the corpus callosum with bilateral extension into the suprasellar cisterns; pathologically, no distinction between dysgerminoma, neuroblastoma, or atypical pineoblastoma could be made. Postoperatively, she exhibited epilepsy, frontal lobe syndrome, and hypothalamic dysfunction, including partial diabetes insipidus, reduced thirst perception, increased appetite, hyperprolactinemia, and poikilothermia. Dependent on ambient temperature, physical activity, and behavioral thermoregulation, core temperature was most of the time between 35.0 and 36.6 °C. On hot summer days core temperature exceeded 40 °C, causing progressive drowsiness, confusion, restlessness, and decreased consciousness; no sweating has been noticed since 1983.

Patient 2 was a 38-year-old woman with no relevant medical history until 1982, when epilepsy, secondary amenorrhea, and poikilothermia were demonstrated. Neuroendocrinologic evaluation revealed no well-known causes of thermolability; CT and MRI of the cerebrum showed no evidence of hypothalamic or pituitary lesions. Core temperature ranged from 31.4 to 35.2 °C and increased up to 38.2 °C during exposure to a hot environment without provoking visible sweating.

Patient 3 was a 34-year-old woman in whom panhypopituitarism and marked thermolability were demonstrated in 1982. MRI of the cerebrum in 1990 showed an empty sella. Core temperature ranged from 32.9 to 37.0; elevation up to 38 °C induced severe discomfort, agitation, confusion, and impaired judgment but no sweating.

Patient 4 was a 31-year-old woman who suffered from epilepsy, post-traumatic encephalopathy, and marked hypothermia after extensive cerebral damage due to a traffic accident at age 16. CT of the cerebrum in 1978 revealed marked central atrophy of the hemispheres, including bilateral thalamic lesions. Core temperature usually varied from 31.7 to 36 °C but increased up to 36 to 37 °C during the 4 months preceding the present study, presumably due to ameliorated control by her environment. Sweat secretion was never observed.

The patients received no anticholinergics or other medication known to interfere with sweat secretion, except for patient 4, who was treated with carbamazepine 200 mg per day throughout this study and clomipramine up to 4 weeks before this study. A more detailed description of the clinical and biochemical data of our patients has been published elsewhere.6

Nine healthy women, matched for age and body mass index, served as controls for the patients; the physical characteristics of all participants are listed in the table. All controls had a normal history of thermal sweating and did not use any medication. To reduce possible effects of the menstrual cycle on the sweat response, all controls and the two nonamenorrheic patients (nos. 1 and 4) were studied during days 5 to 11 of the menstrual cycle. None of the participants was acclimated to heat stress.

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<th>Table. Physical characteristics of subjects</th>
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<td><strong>Controls (n = 9)</strong></td>
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* p < 0.05 (Wilcoxon's rank sum test; controls versus patients).

The experimental procedures were approved by the Local Ethical Committee; informed consent was obtained from all participants.

Investigations. Thermoregulatory sweat test. Preceding heat exposure, baseline values (vide infra) were obtained in a thermonutral climatic chamber (ambient temperature [Taamb] 29 °C, 50% relative humidity) during 50 minutes after a 45-minute acclimatization period. All subjects were investigated in supine position on a comfortable examination table, dressed in bikinis, and were allowed to drink limited amounts of tepid water. The wind velocity was less than 0.1 m/sec.

Assessment of the heat-dissipating capacity was performed during a 180-minute exposure to intense heat stress in a climatic chamber (Ta amb 40 °C, 50% relative humidity). To avoid severe discomfort and heat illness, thermal stress was terminated if rectal temperature (Tr) exceeded 38.5 °C.

To estimate the total weight loss due to sweating, the body weight was recorded on a precision balance (accuracy, ±5 g) preceding and immediately after heat stress, after drying the patient with a towel. The total evaporative weight loss was assessed by continuous recording of changes in total body weight by means of a Potter bed balance (accuracy, ±5 g). Changes in body weight were corrected for intake of liquid as well as respiratory and metabolic weight loss, according to Snellen.14 For 50 minutes before heating and during heat stress, the local evaporation rate was recorded every 10 minutes by means of an evaporimeter15 (Evaporimeter Ep1, ServoMed AB, Stockholm, Sweden) applied to five sites: forehead (a), chest (b), abdomen (c), ventral thigh (d), and ventral forearm (e). Based on the relative areas of body surface of DuBois,16 the weighted mean local evaporation rate (Eva_bod) was calculated according to Eva_bod = 0.1029a + 0.2574b + 0.2974d + 0.1029e.

Rectal temperature was recorded simultaneously by means of a probe with thermistor (depth of insertion, 10 cm) attached to a Squirrel datalogger (type Grant SQ-1201, Grant Instruments Ltd, Barrington, Cambridge CB2 5QZ, England.). Skin temperatures were recorded with thermistors (YSI 409B, Yellow Springs Instrument Co, Yellow Springs, OH) from eight sites: forehead (A), parasternal (B) and para-umbilical (C) regions, medial thigh (D), lateral calf (E), lateral upper arm (F), ventrolateral forearm (G), and hand palm (H). The mean skin temperature (T_skm) was computed according to Gagge and Nishi,17 (with abdomen replacing back): T_skm = 0.07A + 0.175(B + C) + 0.07(F + G) + 0.05H + 0.19D + 0.2E. To calculate the weighted mean skin temperature at the sites of the recording of the Eva_bod (T_skm weighted), the
Acetylcholine test. The response of eccrine sweat glands to intradermally injected acetylcholine was determined at room temperature (T_{amb} ± 22 °C), normal relative humidity, and minimum air convection; both patients and controls (see above) were wearing standard clothing. Local evaporation was recorded continuously by means of an evaporimeter for 10 minutes before and 60 minutes after pharmacologic sweat stimulation. Acetylcholine (0.1%/0.1 ml) was injected on the flexor surface of the forearm (approximately 10 cm distal to the elbow), with an indwelling intradermal 25-gauge needle, by the same investigator in all cases. The epidermis was perforated outside the actual measuring site; the drug was injected after the needle was moved approximately 1 cm intradermally into the test site center. Peak and total (expressed as area under the curve, corrected for baseline values) evaporative responses to acetylcholine were assessed. The rectal and local skin temperatures were recorded with thermistors; due to technical limitations this was performed only in the patients.

To examine the effect of normalization of core temperature on sudomotor function, testing the sweating response to acetylcholine was repeated in two patients (nos. 2 and 3) after several days of steady state normothermia, which was achieved by a higher ambient temperature, increased insulation, and use of an electric blanket.

Pilocarpine test. The sweat response to pilocarpine on the contralateral forearm at the corresponding site was determined simultaneously with acetylcholine testing. Pilocarpine nitrate (Ionto-Pad, Orion Research Inc, Cambridge, MA) 1% was administered by iontophoresis for 5 minutes with 2 mA direct current from an Orion (model 417, Orion Research Inc) potentiometer. Thereafter, the quantity of the sweat response of the stimulated area for 45 minutes was estimated by means of a Macrodust capillary collection device (Wescor Instruments, Logan, UT).

Sweat gland biopsy. To assess whether putative sudomotor dysfunction was related to histopathologic changes, supra-iliac skin biopsies were performed in two patients (nos. 2 and 3).

Statistical analysis. The Wilcoxon rank sum test was applied for comparison of the sweating responses with thermal stress and pilocarpine iontophoresis between patients and control subjects. Regarding the sweating response to acetylcholine, intra- and intergroup comparisons were performed by repeated measures ANOVA with multiple comparison procedures by means of the contrast option of the General Linear Models procedure (SAS Institute Inc, Cary, NC; p value in this case denoted by p*). Values of p < 0.05 were considered to indicate statistical significance. The results are expressed as means ± SD unless indicated otherwise.

Results. Thermoregulatory sweat test. All participants were exposed to heat for 180 minutes; only in patient 2, heat stress was terminated after 120 minutes (due to distress and T_r exceeding 38.6 °C). At the end of thermal stress, both total body weight reduction (646 ± 103 g [range, 459 to 780] versus 101 ± 102 g [range, 26 to 247], p < 0.01) and evaporative weight loss (407 ± 61 g [range, 312 to 530] versus 64 ± 67 g [range, 18 to 162], p < 0.01) were significantly greater in the controls than in the patients.

At thermoneutrality, the local evaporation rate was comparable in the patients and controls (8.6 ± 3.2 g/m² h versus 9.6 ± 2.5 g/m² h, p = ns), despite significantly lower T_r, (35.3 ± 0.3 °C versus 37.0 ± 0.3 °C, p < 0.01) and T_{skin(veg)} (33.2 ± 0.7 °C versus 34.3 ± 0.4 °C, p < 0.05) in the patients. In all controls, sweating started within 5 minutes after the beginning of heat exposure; in contrast, in the patients either no sweating occurred (patient 1) or the sweating response was markedly delayed and reduced. The relation between the onset of sweating and both T_r and T_{skin} is depicted in figure 1. Sweating in patients 2 and 3 started after 60 minutes heating (T_{skin(veg)} 37.7 °C in patient 2 and 37.0 °C in patient 3) and in patient 4 after 130 minutes (T_{skin(veg)} 37.8 °C). The sweat response was limited to the forehead and upper torso in patient 2, whereas patients 3 and 4 showed more generalized thermal sweating. Patient 1 showed no increase in evaporation rate despite core and skin temperatures exceeding 38.5 °C.

Acetylcholine test. The sweating response to intradermal injection of acetylcholine is depicted in figure 2. The evaporation rate in the controls increased significantly from 8.8 ± 3.9 g/m² h to a maximum of 196.9 ± 22.6 g/m² h (range, 170 to 234; p* < 0.0001); compared with baseline value, the evaporation rate remained significantly enhanced during the entire recording.

The evaporation rate in the patients increased significantly after acetylcholine injection from 6.5 ± 4.0 g/m² h to a maximum of 78.5 ± 38.6 g/m² h (range, 32 to 115; p* < 0.05). However, the maximum evaporation rate was significantly decreased in the patients as compared with the controls (p < 0.01); the same applied to the cumulative response to acetylcholine (2,079 ± 1,618 g/m² h [range, 519 to 4,273] versus 6,233 ± 1,048 g/m² h [range, 4,418 to 8,336], p < 0.01). However, at the time of the experiment, T_r in patients 1 to 4 was markedly reduced (35.6, 35.5, 34.2, and 34.4 °C [mean, 34.9 ± 0.7]); the corresponding local skin temperature was 30.1, 30.6, 30.6, and 27.1 °C [mean, 29.6 ± 1.7]). The maximum evaporation rate in the patients was reached at approximately the same time after stimulation as in the controls but was delayed in patient 4.

Normothermia in patients 2 (T_r, 36.9 °C) and 3 (T_r, 35.6 °C) induced a rise of 0.5 °C (patient 2) and 0.7 °C (patient 3) in local skin temperature and an increase in maximum evaporation rate from 32 to 80 g/m² h (patient 2) and from 105 to 134 g/m² h (patient 3).

Pilocarpine test. Pilocarpine iontophoresis induced a secretion of 32.6 ± 11.4 μl (range, 20 to 57.5) sweat in the controls during a 45-minute period. The sweating response to pilocarpine was attenuated in three patients (0 μl, patient 1; 0 μl, patient 2; and 15 μl, patient 3) but markedly enhanced (70 μl) in patient 4. At the time of the test, T_r in the patients 1 to 4 was 35.1, 35.1, 34.2, and 34.4 °C.
Sweat gland biopsy. Histologic examination of skin biopsies in patients 2 and 3 disclosed no abnormalities, particularly no atrophy of eccrine sweat glands.

Discussion. The present study revealed a significant reduction of both thermal sweating capacity and local sudomotor response in our patients, thereby putting them at risk of hyperthermia and potentially severe heat illness. Together with disturbed thermoregulatory mechanisms for heat conservation and heat production, these findings demonstrate that the severely decreased thermosensitivity must be attributed primarily to disorders of the central or preganglionic thermoregulatory pathways.

The hypothalamic control of heat dissipation is governed by the core temperature but modified considerably by the mean and local skin temperature. In the controls, thermal sweating was activated before any significant increase in rectal temperature, presumably due to the immediate rise in skin temperature. In contrast, sweating started only after 60- to 130-minute heating in patients 2, 3, and 4, at remarkably higher mean skin and local skin temperatures (and core temperatures in patients 2 and 4) than in the controls, and patient 1 showed no thermal sweating. Because a rise in mean skin temperature decreases the core temperature threshold of thermal sweating, the apparently normal threshold in rectal temperature in patient 3 may be deceptive. Although we cannot define the exact values, the core and skin temperature thresholds for thermal sweating were markedly increased and the slope of the sweat rate/temperature relation was reduced in at least three patients.

Postganglionic lesions may be distinguished...
from preganglionic or central lesions by testing both the thermoregulatory sweating and sudomotor reflex. The sympathetic sudomotor response to acetylcholine is mediated by both muscarinic and nicotinic receptors, whereas pilocarpine is considered to bind directly to the muscarinic receptor on the eccrine sweat gland.^4,25 Although the sweating response to pilocarpine was markedly blunted or absent in three patients, the positive (although reduced) response to acetylcholine in all patients indicated an at least partly intact local sympathetic supply. Patients with more serious impairment of thermal sweating also showed lower sweating responses to cholinergics. The enhanced sudomotor response to pilocarpine in patient 4, despite reduced thermal and acetylcholine-induced sweating, might be attributed to supersensitivity of the muscarinic mechanisms by carbamazepine or withdrawal of clomipramine.^26

The sudomotor responsiveness to cholinergics is affected by local skin and core temperatures,^4,27,28 notably mediated by the rate of transmitter release at the neuroglandular junction and degree of glandular response.^21 The impaired cholinergic sudomotor response in the patients might be attributable to the reduced core and (local) skin temperature at the time of the test. However, the sudomotor response to acetylcholine in patients 2 and 3 during normothermia remained subnormal. The attenuated sudomotor response might be caused also by impaired secretory capacity or decreased number of active sweat glands due to functional inactivity during prolonged periods of hypothermia, which might be considered as a counterpart of heat acclimatization in thermal sweating after a rise in body temperature. However, no histologic abnormalities were found in sweat gland biopsies. Generalized hypohidrosis and a decreased postganglionic sudomotor response can be caused by generalized autonomic failure, multiple system atrophy, various drugs, and many chronic (skin) disorders^30-34; however, in our patients these causes were not responsible for the sudomotor dysfunction. Therefore, we hypothesize that in addition to the reduced core and local skin temperature, long-standing absence of adequate sudomotor stimulation and possibly secondary degeneration of sudomotor axons may contribute to the acquired sudomotor failure.

Because anhidrosis may easily be misdiagnosed in the case of rapid invisible sweat evaporation,^19 quantitative analysis of sweating capacity is a prerequisite to establish thermoregulatory sudomotor failure, which may occur in combination with an intact cholinergic sudomotor response. Continuous recording of the evaporative weight reduction is adequate to assess total heat dissipation,^17,50 and recording the local evaporation rate at multiple sites makes it possible to assess topographic differences. If inadequate thermoregulatory sweating has been demonstrated despite supranormal temperatures of core and skin, the sudomotor response to cholinergics must be assessed complementarily to differentiate between postganglionic and preganglionic or central lesions. Additionally, sudomotor analysis during prolonged physical exercise may be useful, but this failed to induce an increase in thermal sweating during either hypothermia or normothermia in our patients (unpublished data). Furthermore, impaired heat dissipation can be caused partly by inadequate skin vasodilatation; based on marked reddening of the skin and the high skin blood flow during heat stress,^6 this obviously was not the case in our patients.

The present study has some limitations. First, during thermal stress, core and skin temperatures all changed simultaneously and were recorded intermittently, thereby hampering exact determination of core and skin temperature thresholds for thermal sweating. Second, at the start of heating, rectal and mean skin temperature were lower in the patients; however, even after the onset of thermal sweating, the rate of evaporative weight loss remained much lower in patients than in controls. Third, local skin temperature was not recorded in controls during testing of the cholinergic sudomotor response; however, the local skin temperature of the forearm in the thermoneutral climatic chamber was only 0.7 °C lower in the patients than in the controls, making it unlikely that this variable significantly influenced the differences in sudomotor response. Fourth, the high humidity and low air velocity during heat stress decreased the evaporative capacity. However, based on previously observed absence of visible sweating,^7 the high heat load was necessary to differentiate between anhidrosis or merely elevation of the temperature thresholds for sweating. Furthermore, the exact location of the heterogenic preganglionic lesions remains uncertain, and adaptation of the thermal- and cholinergic-induced sudomotor response to long-standing normothermia requires further elucidation. Thermal sweating and sudomotor responses might be improved by prolonged normothermia, especially if combined with intermittent heat stress, physical training, or drugs that enhance sweating.

Decreased thermostability and hypohidrosis predispose to serious heat illness in a hot environment, especially in combination with physical exercise, inadequate behavioral thermoregulation, dehydration, or chronic (cardiovascular) disorders.^3,4,6,32-35 Recognition of impaired heat tolerance is often difficult,—particularly in patients with poikilothermia who tend to have prolonged hypothermia in cold and moderate climates—but is pivotal for diagnosing poikilothermia and for differentiating between hyperthermia and fever. Because anhidrosis may indicate generalized thermoregulatory failure with potentially serious sequelae,—a careful history and investigation of the sweating capacity and putative precipitating disorders is indicated in hyperthermia without obvious cause. The diagnosis of poikilothermia should be taken into account in patients with decreased thermostability, especially if other autonomic or endocrine disorders exist. In
poikilothermia, considerable fluctuations in core temperature greatly affect physical and neuropsychiatric function, and adequate monitoring of core temperature and amelioration of thermoregulatory behavior may help to prevent serious complications of both hypothermia and hyperthermia.

Our results demonstrate generalized deficiency of thermoregulatory sweating in our patients with acquired poikilothermia, attributable primarily to a defect in the central thermal drive; the impaired postganglionic sudomotor response is partly related to the lower core and skin temperature and possibly also to (longstanding) absence of sudomotor stimulation. We emphasize that a careful history and quantitative assessment of sweating capacity in patients with heat intolerance is essential to recognize serious hydridrosis or generalized thermoregulatory failure and can thereby help to prevent the complications of severe hyperthermia.

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