Neurovascular Function and Sudorimetry in Health and Disease

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Abstract In this review of thermoregulatory function in health and disease, we review the basic mechanisms controlling skin blood flow of the hairy and glabrous skin and illustrate the major differences in blood flow to glabrous skin, which is, in essence, sympathetically mediated, while hairy skin is dependent upon neuropeptidergic signals, nitric oxide, and prostaglandin, among others. Laser Doppler methods of quantification of blood flow—in response to iontophoresis of acetylcholine or heat—and nociceptor-mediated blood flow have relatively uniformly demonstrated an impaired capacity to increase blood flow to the skin in diabetes and in its forerunners, prediabetes and the metabolic syndrome. This reduced capacity is likely to be a significant contributor to the development of foot ulcerations and amputations in diabetes, and means of increasing blood flow are clearly needed. Understanding the pathogenic mechanisms is likely to provide a means of identifying a valuable therapeutic target. Thermoregulatory control of sweating is intimately linked to the autonomic nervous system via sympathetic C fibers, and sweat glands are richly endowed with a neuropeptidergic innervation. Sweating disturbances are prevalent in diabetes and its precursors, and quantification of sweating may be useful as an index of diagnosis of somatic and, probably, autonomic dysfunction. Moreover, quantifying this disturbance in sweating by various methods may be useful in identifying the risk of progression from prediabetes to diabetes, as well as responses to therapeutic intervention. We now have the technological power to take advantage of this physiological arrangement to better understand, monitor, and treat disorders of small nerve fibers and the somatic and autonomic nervous system (ANS). Newer methods of sudomotor function testing are rapid, noninvasive, not technically demanding, and accessible to the outpatient clinic. Whether the potential applications are screening for diabetes, following poorly controlled diabetes subjects during alteration of their treatment regimen, or simply monitoring somatic and autonomic function throughout the course of treatment, sudorimetry can be an invaluable tool for today’s clinicians.

Keywords Sudorimetry · Sweat testing · Sweat gland dysfunction · Thermoregulatory dysfunction · Neurovascular function

Introduction

In this review, we examine the role of the nervous system in the pathogenesis of dysfunction of the neuroregulatory system in diabetes, prediabetes, and the metabolic syndrome. In healthy individuals, heat is dissipated from the body to the environment via the local heat loss mechanisms of skin blood flow (SKBF) and sweating [1]. There are a number of different techniques that address the mechanisms and distribution of SKBF and sweating mechanisms in normal and pathogenic states, and here we examine these in health and disease, focusing particularly on diabetes and, where possible, on the prediabetic state.

Neurovascular Function in Diabetes

While only one study to date has examined whole-body heat loss in individuals with type 2 diabetes [2], several studies have examined the local heat loss responses of SKBF [3–12] and sweating [13–16]. Many of these studies found impairments in local heat loss responses in individuals with type 2 diabetes, as compared with matched controls. Individuals
with diabetes have decreased vasodilator responses to pharmacological stimuli [4, 7, 10]. Whereas Williams et al. found decreased forearm blood flow to both endothelial-dependent and direct nitric oxide (NO) application [4], we found that the NO response was relatively intact and that there was overproduction of cutaneous NO but impaired responses to endothelial- and prostacyclin-dependent mechanisms of vasodilation [17–19]. In patients with type 2 diabetes, we found impairment of blood flow response to 45 °C heat stimuli [17–19], and Schmiedel found impaired responses to heat, acetylcholine, and NO donor sodium nitroprusside [7, 10]. We [17–19] examined the blood flow in the hairy and glabrous forearm skin in patients with type 2 diabetes, since the two have very different autonomic and neuropeptidergic regulation [3, 19]. It is likely that the studies done by Schmiedel included patients with more advanced disease. Figure 1 illustrates the method employed in our laboratory to examine blood flow using laser Doppler flowmetry quantification in response to a variety of stimuli in both glabrous and hairy skin and the targets being evaluated.

Indeed, the major defects are found in the hairy skin regulated by the neupeptidergic nervous system [3]; furthermore, the reduction in heat-mediated vasodilation occurs in relatives of patients with diabetes and in patients with impaired glucose tolerance (IGT) (Fig. 2). A similar impairment of vasodilation is found in type 2 diabetes when the core temperature is elevated [11]. It seems, then, that the whole heat transfer mechanism is defective in prediabetes and diabetes and that one could anticipate that situations demanding heat dissipation, such as exercise, might be compromised. We examined people with type 2 diabetes who had engaged in a regular exercise program and showed that chronic exercise had elevated SKBF to near normal in the basal state [20]. The response to 44 °C heating was also impaired in the participants with diabetes, as compared with the nondiabetic controls [20], but could be improved by exercise on a bicycle ergometer to fatigue levels [21]. There was an inverse relationship between SKBF and fasting glucose levels and Hemoglobin A1C, suggesting that chronic exercise and diabetes control improve SKBF [20, 21]. We further sought to determine the impact of training duration and the type of exercise on SKBF. Ten weeks of aerobic training thrice weekly improved SKBF on the dorsum of the foot without improving VO₂ max [22]. Whereas 2 months of resistance exercise did not increase maximal SKBF on the dorsum of the foot [23], we felt that there was something about the chronic exerciser that had escaped the impact of short-term studies. Cohen and colleagues [24] showed that a 14-month resistance exercise program improved endothelial function in diabetes. Da Silva and colleagues [25] showed that high-intensity aerobic exercise 4 times a week at 80 % maximum heart rate (HR) improved the dysfunction in metabolic syndrome [25], whereas similar exercise in diabetes at 55 % of maximum HR did not. Thus, it seems that control of the thermoregulatory sweating process is defective in the metabolic syndrome, IGT, and diabetes, but the defect is functional and not necessarily structural, inasmuch as it can be improved with intense exercise, be it aerobic or strength training for an extended period. How these abnormalities affect whole-body heat balance and what the regulatory mechanisms are remain unclear.

**Sweating in Diabetes**

Ninety-four percent of people with type 1 and type 2 diabetes with signs and symptoms of neuropathy have impaired sweating responses to ambient heat of 44 °C with 45 % humidity [14]. Lower sweat rates were also found in type 2 diabetic patients using handgrip at 40 % of maximum HR to exhaustion at an ambient temperature of 32 °C [13], in contrast to the increased sweating of the forehead. Regional differences may thus be important, since patients with autonomic neuropathy are known to have dry feet and sweat from their foreheads to dissipate heat [26]. What remains to be established is the role
of the ANS or structural changes in sweat glands. Long-standing, poorly controlled type 2 diabetes leads to impairment of sudomotor function linked to loss of peripheral sweat gland properties [14, 27]. Both the innervation of sweat glands measured as an index (area of normalized fibers/area of sweat glands), as compared with normal controls [27, 28], and the sweat gland coil innervation are reduced. Thus, the consensus would appear to be that defects in sweating occur in the metabolic syndrome and IGT before the advent of diabetes. Obesity impacts SKBF and, in all the studies reported there, is an additional component of diabetes superimposed on obesity, which reduces SKBF further [3, 5, 6, 10, 11, 21]. The dyslipidemia of the metabolic syndrome is associated with reduction in IENF [29]; statins improve blood flow [30], as do rosiglitazone [31] and pioglitazone [32], by mechanisms that are diametrically different from NO production and may involve the pleiotropic actions of the statins and the thiazolidinediones [17–19]. Studies using PPAR alpha antagonists have been shown to improve findings of neuropathy [33]. Furthermore, hypertension is a common covariate of diabetes and the metabolic syndrome. Cranberry et al. [34] found that maximal SKBF in hypertensive individuals was reduced, as compared with age- and weight-matched controls [34], while Kenney et al. showed attenuated responses in hypertensive subjects performing exercise of moderate intensity (40 % VO2 max) in heat of 38 °C [35, 36]. These findings are compatible with changes in the microvasculature of people with diabetes. To address this, Jaap et al. [37] compared maximal SKBF response of the foot dorsum to local heating to 44 °C in hypertensive type 2 diabetes, normotensive type 2 diabetes, and normotensive nondiabetes groups. SKBF response to local heating was comparable between the hypertensive and normotensive diabetic participants, but diabetes in both groups exerted an attenuating effect on SKBF [37]. In addition to the decrements shown in inactive individuals, aging [38, 39] and gender impact the ability to increase blood flow and sweating [40], with females having less ability to sweat than males. Of course, there are marked differences in the capacity of individuals to sweat even within families. Apart from our research [41], most studies have failed to take cognizance of the effects of age, gender, physical fitness, and neurological status on SKBF and the ability to sweat. Of greatest importance to this treatise is the ability to dissect the role of sweating, SKBF, and measures that can be applied in the clinic that give meaningful data on distribution of sweating impairment and may have relevance to the metabolic syndrome, IGT, and the progression to diabetes.

The Sweat Gland

The human body is covered with somewhere between 2 and 4 million eccrine sweat glands, distributed over nearly the entire body surface. They are most numerous on the soles, forehead, axilla, palms, and cheeks [42]. The sweat gland is a tubular structure with a coiled secretory portion in the deep dermis or hypodermis and a straight duct leading to the skin surface. The clear cells of the coiled portion secrete the major components of sweat—mainly, water, sodium, chloride, and other minor electrolytes [42] (Fig. 3).

Sweating is one component of thermoregulation controlled by the sympathetic nervous system. The central thermoregulatory center is located in the hypothalamus and integrates thermal information from central (preoptic anterior hypothalamus) and peripheral (skin, viscera, spinal cord) thermoreceptors [43]. In response to an increase in body temperature, the hypothalamus sends signals via the preganglionic sympathetic nerves, which synapse in the paravertebral ganglia. Postganglionic axons then relay the signal, releasing acetylcholine (Ach) from presynaptic nerve endings to bind to M3 muscarinic receptors on the clear cells of eccrine sweat glands [42, 43]. Activation of the clear cell receptors triggers an influx of extracellular calcium into the cytoplasm, causing an efflux of potassium chloride from the cell, followed by water. In the complex process of cell repolarization, sodium (Na), potassium (K), and chloride (Cl) ions exchange across both the basolateral and luminal membranes of the sweat gland cells. The end result is an efflux of Cl, followed by Na, into the sweat gland lumen and the formation of an isotonic sweat fluid. Some NaCl is eventually reabsorbed along the sweat gland coiled duct, in an effort to preserve electrolytes, before sweat secretion at the skin surface [42].

Interestingly, a stimulated sweat gland can also trigger a sudomotor axon reflex, wherein a cholinergic agonist (such as acetylcholine) applied to the skin will bind to the muscarinic receptors of one sweat gland, as well as the nicotinic receptors on nerve terminals of the sudomotor fibers, generating an impulse antidromically. At nerve branch points, the impulse will then travel down neighboring sympathetic nerve fibers and lead to sweat production from the surrounding sweat glands [43]. This reflex is used as the mechanism for sudomotor function testing (SFT) in a number of tests (quantitative sudomotor axon reflex testing [QSART], for example).

The sweat glands are innervated by the sympathetic nervous system and are part of the fight or flight response system. Their innervation consists of two parts, a preganglionic and a postganglionic neuron. The preganglionic neuron is short, originates from the thoracolumbar region of the spinal cord, uses acetylcholine as its neurotransmitter, and synapses with the postganglionic neuron via a nicotinic acetylcholine receptor. The postganglionic neuron for sweat gland innervation differs from other sympathetic postganglionic neurons in that it releases acetylcholine to act on muscarinic receptors; all other sympathetic postganglionic neurons, with the exception of the adrenal medulla, use norepinephrine.
The developing sweat gland innervation shows the appearance of two cholinergic markers, vesicular acetylcholine transporter (VACHT) and acetylcholinesterase activity. VACHT is an excellent indicator of cholinergic function because the coding sequence for VACHT, which transports acetylcholine into synaptic vesicles, resides within the first intron of the choline acetyltransferase (ChAT) gene [44, 45], and expression of the two genes is coordinately regulated in sympathetic neurons [46, 47]. In addition to cholinergic markers, the mature sweat gland innervation contains immunoreactivity for two neuropeptides, vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP). VIP is induced in sympathetic neurons by cholinergic differentiation factors in vitro [48, 49] and by sweat glands in vivo [50, 51].

Particularities of the autonomic sympathetic nerve fibers that innervate sweat glands are that they are long (the postganglionic nerves start at the spinal cord and may end at the palm or sole), thin, unmyelinated, or thinly myelinated C fibers. Because of these characteristics, they are prone to damage early in many neuropathic processes; assessing sweat gland nerve function, or dysfunction, therefore, can be used as a surrogate for the damage imparted to small caliber sensory nerves in neuropathy. The majority of diabetic peripheral neuropathies, for example, are length-dependent, symmetrical sensorimotor polyneuropathies in which the onset is insidious. However, it could be evaluated early in the course of the disease through the assessment of sudomotor function.

**Sudomotor Function Testing: The Science, Clinical Applications, and Prospects for Preventive, Diagnostic, and Clinical Care**

Abnormalities in sudomotor function in diabetic patients were clinically measurable as early as the 1980s and were noted to correlate with the presence of autonomic neuropathy [14]. The various techniques of SFT, although each has its strengths and weaknesses, are very sensitive and specific in the detection of distal small-fiber neuropathy. SFT, however, has remained underutilized in clinical practice, due to lack of availability, technical demands of the tests, and result variability.

New technology, however, promises not only easy accessibility to SFT, but also powerful new clinical applications. Small-fiber and autonomic neuropathies are leading complications of a number of disease states or side effects of their treatment; both can now be rapidly detected and evaluated with SFT—in many cases, prior to any other clinically measurable sign.
The Sudomotor Axon Reflex

Cholinergic agonists such as acetylcholine and pilocarpine applied through iontophoresis bind to muscarinic receptors on sweat glands, causing local sweat production, but simultaneously bind to nicotinic acid receptors on the terminal of nerve fibers. The impulse will travel antidromically along the nerve fiber (Fig. 4) until reaching a branch point, where it will then travel orthodromically to a neighboring population of eccrine sweat glands, causing an indirect mediated sweat response. The complexity of the regulation of neurally mediated sweating can now be evaluated more directly with electrical stimulation, as shown below. However, the issues arise with regard to the role of neuropeptides (e.g., CGRP), the pathways involved in nociceptive stimulation (e.g., TRPV1), and the mechanism of activation of thermally mediated sweating, which may invoke mechanisms related to blood flow, as well as the sweat gland mass and integrity of their innervation.

Clinical and Research Uses of Sudomotor Function Testing

Sweat gland function testing, up until recently, was mainly used in the clinical setting for the diagnosis (or confirmation) of cystic fibrosis. A quantitative pilocarpine iontophoresis sweat chloride test remains the gold standard in the diagnosis of cystic fibrosis and is recommended even following the identification of two cystic fibrosis transmembrane conductance regulator gene mutations in an individual [52]. Performance of an accurate sweat test, however, demands adherence to a specific methodology by a certified laboratory; proper interpretation of the test is also critical [52, 53].

Nonetheless, critical new applications are now being recognized for SFT—in both clinical and research settings—and should permit an expansion of this diagnostic modality across the medical community. From a physiological standpoint, the pattern of innervation of sweat glands—namely, the postganglionic sympathetic nerve fibers—is allowing clinicians and researchers to use SFT to assess dysfunction of the peripheral and autonomic (sympathetic) nervous systems. Sweat gland testing holds a number of advantages, as compared with other forms of neuropathy assessment methods: The sweat glands, appearing at the surface of the skin, are easily accessible for testing; certain testing methods are completely objective, not requiring patient preparation or special cooperation; and sudomotor dysfunction is a common finding in a number of neuropathies and one of the earliest detectable abnormalities [43]. SFT as assessed with QSART correlates well with intraepidermal nerve fiber density (IENFD) from skin biopsies [54], which is considered one of the most objective quantitative measures of peripheral neuropathy [55-56]. IENFD is used to investigate somatic unmyelinated intraepidermal nerve fibers, dermal myelinated nerve fibers, and autonomic nerve fibers—hence, the correlation with QSART, which measures the function of sweat gland autonomic nerves [57]. Similarly, sweat gland nerve fiber density (SGNFD) correlates with the Neuropathy Impairment Score in the Lower Limb (NIS-LL) and the Michigan Neuropathy Screening Instrument (MNSI) [58]. Furthermore, Gibbons et al. demonstrated, using capsaicin to provoke degeneration of cutaneous nerve fibers, that (1) there is a definite correlation between structural and functional damage induced in both sensory and autonomic nerve fibers by capsaicin; (2) the autonomic nerve fibers, although also damaged by capsaicin, suffer somewhat less profound degeneration and more rapid recovery than small sensory nerve fibers but follow a parallel course of degeneration and recovery; and (3) sweat gland nerve fiber density correlates with the functional damage and is, therefore, a valid indicator of autonomic dysfunction [59]. Sudomotor dysfunction can occur in a number of chronic conditions and, if identified early, may be critical in detecting abnormalities of the peripheral and/or autonomic nervous systems, allowing for earlier intervention and a reduction in consequent morbidity and mortality. In addition, since the recovery of autonomic nerve fibers is quicker than that of sensory nerves, SFT could be used as an early indicator of treatment efficacy in neuropathy.

Peripheral Neuropathy

Polyneuropathies are common, often involve predominantly small nerve fibers, and usually present with patients reporting pain [60]. They may occur secondary to diabetes, glucose intolerance, toxins (e.g., alcohol), HIV, connective tissue disease, sarcoidosis, drugs (antiretrovirals, chemotherapeutic agents), and idiopathy [60, 61]. In diabetes, sensorimotor polyneuropathy (DSPN) is the most common type, affecting about 25% of patients with diabetes in the community [62]. There is loss of small-fiber-mediated sensation (thermal and pain perception), as well as large-fiber impairment (loss of touch and vibration perception). There may also be “positive” symptoms, such as numbness, paresthesias, and pain. The
course of DSPN is insidious, though, and up to 50 % of patients with neuropathy may be asymptomatic [63•], often resulting in delayed diagnosis. Advanced or painful DSPN, however, may result not only in reduced quality of life, but also in considerable morbidity and mortality. It is accepted that DSPN develops alongside longstanding hyperglycemia, metabolic derangements, and cardiovascular (CV) risk factors [55••]. Furthermore, DSPN has been shown to be statistically associated with retinopathy and nephropathy [55••] and may occur concurrently with autonomic neuropathy [64]. In diabetic peripheral neuropathy, sudomotor dysfunction may, in itself, result in dryness of the foot skin and has been associated with foot ulceration [55••].

Currently, expert panels have recommended nerve conduction (NC) testing for the diagnosis of DSPN in epidemiological surveys or clinical trials, “as an early and reliable indicator of the occurrence of this neuropathy” and “the minimal criteria for the diagnosis of DSPN” [55••]. The same panel, however, also recognized that if NC is normal, a validated measure of small-fiber neuropathy (with class 1 evidence) may be used to confirm DSPN. An interesting study was recently published comparing the change in DSPN in a group of diabetic patients from baseline to 6 months, using IENFD, NC, and other tests. Only IENFD (a measure of small nerve fiber) showed significant change over the 6-month period and could demonstrate progression of DSPN [65]. Considering that large-nerve-fiber tests (such as NC tests) may remain normal until neuropathy is quite advanced, SFT—which measures small-nerve-fiber function—holds a temporal advantage in the diagnosis of peripheral polyneuropathies.

It has been shown that small-fiber measurements of IENFD, warm thermal perception, and sudomometry are more sensitive than large-fiber measures in identification of neuropathy and are the best predictors of development of more florid features of neuropathy [66]. This is particularly important in patients with metabolic syndrome, IGT, and IFG, which may go undiagnosed without resort to skin biopsy, since the small-fiber neuropathies are often silent with normal strength, reflexes, and NCs [17, 29, 67].

Autonomic Neuropathy

Sweat gland sympathetic nerve fiber function not only parallels small-nerve-fiber function in peripheral neuropathies, but these same nerves are an integral part of the ANS. The ANS is the primary extrinsic control mechanism regulating HR, blood pressure, and myocardial contractility [68, 69•]. Cardiac autonomic neuropathy (CAN) describes a dysfunction of the ANS and its regulation of the CV system. CAN is now recognized as a serious and widespread complication of diabetes mellitus, systemic amyloidosis, and a variety of neurological disorders such as seizures, strokes, mass lesions, and multiple sclerosis [54]. In the diabetes population, the prevalence of CAN varies from 2.5 % to 50 % [55••, 64]; in the EURODIAB IDDM Complications study, it was calculated to be 36 % [68]. CAN is implicated as the cause for an approximately fivefold risk of mortality in diabetes patients [68]; a large body of evidence demonstrates that CAN is the strongest predictor for mortality in diabetes mellitus, independently of baseline CV disease (CVD), diabetes duration, traditional CVD risk factors, and medications [70–72]. CAN also results in serious and costly morbidities (silent myocardial infarction, coronary artery disease, stroke, progression of diabetic nephropathy, and perioperative complications) [26, 55••, 63•].

Because early symptoms of CAN tend to be nonspecific and less evident than those of peripheral neuropathy—and because CAN may occur independently of peripheral neuropathy [64]—its diagnosis is frequently delayed or may never occur before the occurrence of a catastrophic event. Today, there are well-established, noninvasive testing methods to detect and monitor CAN, and, because of the large number of affected patients, screening for CAN should be routinely considered. Rhythmic tachycardia (HR of 100–130 bpm) occurs at an advanced stage of CAN; therefore, detection of subclinical (asymptomatic) CAN should be the goal for every clinician. Tesfaye et al. suggested screening for CAN at the time of diagnosis for type 2 diabetes and 5 years after diagnosis for type 1 diabetes, or earlier for patients at greater risk [55••]. There may even be a role for more aggressive screening, since subclinical CAN may occur in patients with IGT, years prior to the development of overt diabetes [63•]. Beyond diagnosis, testing for CAN may distinguish between static and progressive disorders, as well as treatment response over time [54].

Evaluation of CAN must assess the three components of the autonomic system: cardiovagal (parasympathetic), adrenergic (sympathetic), and sudomotor (sweating) functions. Kempler suggests using corrected QT intervals measured on the electrocardiogram—a specific, albeit insensitive, indicator of autonomic dysfunction—as a screening test to select patients for more extensive CAN evaluation [68]. Standardized testing batteries have been described in a number of consensus statements [73–75]. Proceedings from a consensus conference in 1992 recommended that three tests (R-R variation, Valsalva maneuver, and postural blood pressure testing) be used for longitudinal testing of the CV autonomic system [64].

In-depth descriptions of the cardiovagal and adrenergic testing methods for CAN can be found elsewhere [54, 64, 69•]. Assessment of sudomotor function provides a measure of the sympathetic cholinergic function in the workup of CAN. Although some sweat gland testing methods may not distinguish between pre- and postganglionic nerve fibers, this does not obviate the fact that sudomotor dysfunction is one of the earliest findings in distal small-fiber neuropathy and correlates closely with the presence of CAN [76]. QSART has been found to be the most sensitive physiologic autonomic test in
small-fiber neuropathy, with a sensitivity of 75–90 % [60]. Fealey conducted a thermoregulatory sweat test (TST), a very rigorous method for assessing sudomotor function, on 51 patients with diabetes and clinical neuropathy and demonstrated that the percentage of body surface anhidrosis correlates with the degree of autonomic dysfunction [14].

These new applications warrant not only an understanding of the techniques available for sweat gland function testing, but also the introduction of SFT into the current practice paradigm by using testing modalities whose ease of use and reproducibility allow widespread access in the medical community.

Current Techniques of Sudomotor Function Testing

There now exist several reliable and validated techniques of SFT; however, most have been underutilized in the clinical setting. Some of these techniques require not only specialized equipment, but also patient preparation and trained technicians for test performance and/or interpretation, as well as prolonged testing time.

Available techniques include TST, QSART, silicone impressions, sympathetic skin response (SSR), acetylcholine sweat-spot test, quantitative direct and indirect axon reflex testing (QDIRT), Neuropad, SGNFD, and SUDOSCAN. An in-depth review of the details of these techniques has been recently published by Illigens and Gibbons [43]; therefore, only the highlights of SFT methods, with their advantages and challenges, will be mentioned below.

TST assesses sweat output over the anterior body surface in response to a heat stimulus; it has the ability to evaluate the integrity of central and peripheral sympathetic sudomotor pathways. The subject lies supine and unclothed in a temperature- and humidity-controlled chamber; an indicator dye is applied to the skin, along with multiple temperature probes. As core body temperature is raised, sweat produces a change in local pH, resulting in indicator dye color change. Areas of sweat dysfunction are visible as a lack of dye color change. TST can show specific areas of sudomotor dysfunction on the anterior surface of the body and an index of severity of autonomic dysfunction. It cannot, however, differentiate between pre- and postganglionic lesions without the use of additional tests; and it requires substantial equipment that has limited availability, patient preparation, proper interpretation of normal variants, and time [43, 54].

QSART is currently the most widely available SFT method. Four testing sites are used (forearm, proximal leg, distal leg, and dorsum of the foot). Ten percent acetylcholine fills the outer ring of a QSART capsule, which is applied to the skin. As the cholinergic agent is iontophoresed, the sweating induced is captured in the inner chamber of the capsule, and the resulting change in humidity is measured by a hygrometer. QSART can measure maximal sweat output, as well as sweat onset latency. It is reproducible (although there have been inconsistent results) [77], has a sensitivity of 75–90 % for small-fiber neuropathies, and often correlates with IENFD [54, 60]. Specifically, Low et al. demonstrated that QSART is sensitive enough to test patients with distal small-fiber neuropathy without or with mild conduction abnormalities [57]. However, a number of drawbacks have kept QSART from widespread clinical utilization: It can assess only the postganglionic sudomotor response; the patient has to be adequately prepared and not taking medications with anticholinergic effects; the test can be time consuming and requires expensive and specialized equipment; test performance requires a trained technician; and four sites on the body must be tested [43].

Silicone impressions utilize the same cholinergic iontophoresis principle as QSART to assess sudomotor response. Acetylcholine, pilocarpine, or methacholine is iontophoresed into the skin for 5 min; then a thin layer of silicone dental impression material or a similar rapid-setting polymer is applied to the area of examination. The sweat droplets resulting from the cholinergic agent produce imprints into the silicone; these droplets can be analyzed for size, number, and distribution digitally or under light microscopy. Silicone impressions are a simple SFT method, but its limitations reduce its use. Dirt, hair, skin texture, and even rubber gloves may produce artifacts; only postganglionic sympathetic nerve function can be assessed; and newer dental impression material produce lesser impression defects, so that novel polymers have been devised to make this test viable [43].

Both the acetylcholine sweat-spot test and QDIRT measure postganglionic sympathetic sudomotor function using a cholinergic stimulus. For the sweat-spot test, the skin is initially painted with reagent dye; acetylcholine is then injected intradermally, and the resulting sweat droplets can be visually quantified. The injection of acetylcholine for sweat-spots may be painful and unacceptable to patients.

For QDIRT, a cholinergic agent is iontophoresed into the skin; then a reagent dye is applied, and pictures are taken over a 7-min period, allowing digital quantification of direct and indirect sweat production. QDIRT is relatively rapid and noninvasive, and it correlates well with silicone impressions. However, QDIRT can be quite sensitive to ambient temperature, humidity, patient hydration, tobacco consumption, and caffeine intake [78].

SSR measures a change in the skin electrical potential in response to an arousal stimulus or an electric shock. Electrodes are placed on the hand, forearm, proximal leg, distal leg, or proximal foot, and responses (amplitude and latency) are recorded with an EMG. SSR methodology is simple and assesses a polysynaptic reflex (spinal, bulbar, and suprabulbar); it may therefore detect abnormalities in a variety of neurological disorders, including central nervous system degeneration. The source of the skin’s electrical potential is unclear but is attributed to sweat glands and the epidermis; therefore, SSR is only a
surrogate measure of sympathetic cholinergic sudomotor function. Also, SSR can vary widely within and between patients and may be insensitive with older age and mild autonomic dysfunction [43, 54, 60].

The Neuropad® is a simple noninvasive visual indicator test to evaluate sympathetic autonomic neuropathy (sweating) in the diabetic foot. The results of testing correlate with Neurologic Symptom Score (NSS), Neuropathy Disability Score (NDS), Quantitative Sensory Testing (QST), and autonomic function testing, as well as IENFD, and predict risk of foot ulceration [79, 80].

Sudorimetry

In developing newer SFT technology, the focus has been placed on ease of use (such as SSR) combined with high reproducibility regardless of environmental or patient factors. SUDOSCAN, similarly to SSR, makes use of the easily measured electrical potential of sweat glands to assess sudomotor function. In contrast to SSR, SUDOSCAN directly evaluates sweat gland function: It uses direct current (DC) stimulation and reverse iontophoresis to measure the local conductance derived from the electrochemical reaction between sweat chloride ions and the nickel included in the stainless steel electrodes. The patient stands, placing both palms and both soles on nickel electrode plates, while low-voltage DC combinations are applied over a course of 2 min as a stress test of the glands’ ability to release chloride ions. The output reading is electrochemical sweat conductance (ESC): the ratio of the current measured over the constant power applied expressed in microSiemens(μS). The lower the ESC, the greater the sudomotor impairment—that is, dysfunction of the sympathetic C fibers innervating sweat glands. SUDOSCAN testing is entirely painless, can be conducted in 3 min, and requires no special patient or equipment preparation. Test administration and result interpretation also demand no special training [82, 83]. It is objective, reproducible, and quantitative, requiring no patient cooperation. It is recommended, however, that SUDOSCAN testing on patients who suffer from seizures or have implanted electrical medical devices be conducted in the presence of a medical doctor.

Correlation of ESC with other measures of neuropathy and CAN assessment have been impressive: Yajnik et al. performed various neuropathy assessments on 265 diabetic patients and found that ESC measurements between the left and right sides varied by 9.5 % for hands and 6.0 % for feet (it was 14.2 % for vibration perception test [VPT]); lower ESC was significantly associated with increasing symptoms on MNSI A, increasing physical abnormalities on MNSI B, and increasing score on VPT. Even more compelling was the finding that patients with ESC<40 μS were more than 4 times as likely as patients with ESC≥40 μS to have two or more abnormal CAN tests (OR=4.41 [1.72–11.29]). Lower ESC was specifically associated with postural fall in blood pressure, a measure of sympathetic CAN [82].

Sensitivity, specificity, and reproducibility of SUDOSCAN were measured among 133 type 2 diabetes patients, as compared with 41 healthy controls. ESC values had a sensitivity of 75 % and a specificity of 100 %, with an area under the receiver operating characteristic (ROC) curve of 0.88 at a threshold of 50 μS; coefficients of variation in hand and foot measurements were 15 % and 7 %, respectively [84]. A similar study among 142 French diabetic patients showed that descending foot ESC measurements from 66±17 to 43±39 μS correlated to increasing VPT threshold from <15 to >25 V (p=.001), regardless of blood glucose levels [85]. Efficiency of sweat measurement has been examined using ROC curve analysis. At a VDT of 21 V, the AUC was 71 %, and the sensitivity and specificity calculated on the continuous ESC scale were 73 % and 62 % at an ESC of 52 μS. Lower ESC was associated with increasing symptoms (MNSI A; r=.12, p=.05), increased physical findings (MNSI B; r=.26, p<.01), and increasing VDT (r=.23, p<.01). Furthermore,
patients with an ESC score of <40 uS had an OR of >2 for objective neuropathy (MNSI B) and an OR of 3.97 for VDT of >25 V and were more than 4 times likely to have an abnormal CAN test, with an Odds Ratio (OR) of 4.41. However, of the CAN tests, only the postural fall in BP was weakly associated with lower ESC ($r= -0.17, p < 0.05$) [82]. These data do support the notion that Sudoscan is a measure of peripheral somatic small-nerve-fiber function but may not relate to CAN except when far advanced with the development of clear sympathetic dysfunction, which occurs late in the evolution of autonomic neuropathy [26].

Our group compared 210 healthy controls with 78 diabetic patients with and without neuropathy. ESC of hands and feet was significantly decreased in patients with diabetic neuropathy, when compared with healthy controls and diabetes mellitus patients without neuropathy ($56.33\pm1.63$ vs. $84.41\pm0.88$ and $75.86\pm2.99$, respectively, for feet ESC; $p<0.0001$). Diabetes mellitus patients with painful diabetic neuropathy had significantly worse ESC of their feet than did patients with nonpainful diabetic neuropathy ($52.8\pm3.6$ vs. $68\pm6.6$, $p<0.05$). Sudoscan results correlate significantly with clinical measures of neuropathy, somatic and autonomic function testing, and pain scores. An association was detected between NIS-LL scores and ESC in the feet. Increasing NIS-LL scores were associated with decreasing ESC. On an ROC curve analysis, Sudoscan showed a sensitivity of 78% and a specificity of 92%, equivalent to the one shown for clinical neuropathy scores (Table 1). Test–retest reliability in 112 healthy controls before and after a VO2 max test was excellent for the feet, with a correlation coefficient of .8 ($p<0.0001$). (These data have not been published.)

Sudomotor Function Testing

Sudoscan was used to measure ESC on the hands and feet of 41 CF adults and 20 healthy controls. The increased

### Table 1: Diagnostic efficiency of feet and hands electrochemical sweat conductance (ESC) to reflect diabetic neuropathy

<table>
<thead>
<tr>
<th>Criterion*</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>$+LR$</th>
<th>$-LR$</th>
<th>$+PV$</th>
<th>$-PV$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hands ESC</td>
<td>64</td>
<td>78.33</td>
<td>85.71</td>
<td>5.48</td>
<td>0.25</td>
<td>61.04</td>
</tr>
<tr>
<td>Feet ESC</td>
<td>77</td>
<td>78.34</td>
<td>92.38</td>
<td>10.28</td>
<td>0.23</td>
<td>74.6</td>
</tr>
<tr>
<td>NIS-LL</td>
<td>1.5</td>
<td>76.67</td>
<td>85.71</td>
<td>5.37</td>
<td>0.27</td>
<td>95.83</td>
</tr>
</tbody>
</table>

NIS-LL: Neuropathy Impairment Score in the Lower Limb, $+LR$: positive likelihood ratio, $-LR$: negative likelihood ratio, $+PV$: positive predictive value, $-PV$: negative predictive value

*Criterion corresponding with highest Youden index

Invasive and labor intensive, making it relatively impractical for large population-based sudomotor function assessments [28, 86]. Figure 5 shows a sweat gland stained with antibody to the pan neuronal antigen. On the left is a normal sweat gland, and on the right is one showing depletion of nerve fibers.

The situation is a little more complex, since sweat glands also receive innervation from a number of neuropeptides. Figure 6 shows a sweat gland with normal neuropeptidergic innervation and one from a patient with long-standing diabetes showing a relative increase in calcitonin G related peptide innervation.

Current Clinical Applications and Research Areas for Sudomotor Function Testing

Minimum criteria for the clinical diagnosis of diabetic sensorimotor polyneuropathy (DSPN), according to the American Academy of Neurology, are a positive nerve symptom score and evidence of neurologic impairment demonstrated by a positive score using the nerve impairment scoring system. This results in the exclusion of large numbers of patients, including those with signs of neuropathy but no symptoms and those with neuropathic symptoms but no signs [63•]. Similarly, autonomic neuropathy is most commonly diagnosed when symptoms and clinical signs are quite advanced—that is, resting tachycardia, orthostatic hypotension, or exercise intolerance in the case of CAN; constipation, diarrhea, or gastroparesis in the case of GI dysfunction; or erectile or bladder dysfunction in the case of genitourinary involvement [64]. With recent technological advancement in SFT and ongoing research into its use in neuropathy, clinicians should feel compelled to screen and follow up patients aggressively if progress is to be made in reducing the mortality and morbidity associated with peripheral and autonomic dysfunction.

Up until now, SFT in the clinical setting has been used mainly in the diagnosis of cystic fibrosis (CF) and other disorders of sudomotor function (e.g., hyperhidrosis) and as a supporting diagnostic test in autonomic dysfunction along with cardiovagal (parasympathetic) and adrenergic (sympathetic) function tests—for example, as one component of the 10-point composite autonomic scale [60]. Another not infrequent condition in patients with autonomic neuropathy in which SFT has a role is a complaint of excessive proximal sweating often caused by impaired distal sweating; SFT in this last scenario can diagnose sweat gland dysfunction and its concurrent autonomic component.

Cystic Fibrosis

In the domain of CF, newer SFT technology has been demonstrated to be accurate in confirming the diagnosis: SUDOSCAN was used to measure ESC on the hands and feet of 41 CF adults and 20 healthy controls. The increased
sweat chloride concentration in CF patients resulted in ESC measurements that were significantly higher in CF patients, as compared with healthy adults (75±10 μSi vs. 62±13 μSi; \(p<.0001\)). dESC (which takes into account ESC obtained when low and high voltages are applied) was even more accurate, with a diagnostic specificity of 1 and a sensitivity of 0.93. The ease of application of SUDOSCAN opens many opportunities for further use in CF: ESC results need to be correlated with sweat chloride concentration; SUDOSCAN needs to be investigated in different CF phenotypes and in children; and ESC may eventually be used to follow outcomes in CF drug development or CF long-term treatment [53].

Peripheral and Autonomic Neuropathy

The CV autonomic reflex tests are the gold standard for clinical autonomic testing. They essentially measure HR and blood pressure changes during provocative physiological maneuvers. These tests are noninvasive and safe but have several limitations: Responses may be altered by a number of factors, such as caffeine, tobacco products, food, exercise, or medications; they are age dependent; and normative data for the specific technique employed must be used for result interpretation [54, 69]. SFT—and in particular, newer techniques such as SUDOSCAN—may allow wider clinical screening for CAN.

Fig. 5 Normal (left) and depleted (right) sweat glands stained with PGP 9.5

Fig. 6 Sweat glands from a nondiabetic (top) woman and a diabetic (bottom) woman, showing increased levels of calcitonin G-related peptide (green staining)
and assessment of treatment response. Furthermore, autonomic testing may complement evaluation of polyneuropathy: It may document the presence of neuropathy in patients with painful small-fiber sensory neuropathy in which clinical signs are absent [54]. Conversely, in patient with diabetes and DSPN, subclinical autonomic neuropathy may coexist, and its diagnosis is critical if mortality risk is to be reduced.

Fealey demonstrated in 1989 that an increasingly abnormal TST in diabetic patients correlated not only with peripheral neuropathy, but also with worsening autonomic neuropathy [14]. With newer technology, making the diagnosis and following the progression or response to treatment of autonomic neuropathy is greatly facilitated. ESC results measured in diabetic patients with a 2-min SUDOSCAN test were significantly associated with measures of peripheral neuropathy (MNSI, VPT), as well as cardiac sympathetic dysfunction [82, 85]. Such rapid testing is ideal for widespread screening for neuropathy in the clinical setting.

Prediabetes and Metabolic Syndrome

It is well-known that neuropathy can occur in persons suffering from IGT or metabolic syndrome, years prior to a diagnosis of diabetes mellitus. These patients may be symptomatic or asymptomatic and have normal or abnormal NC velocities (a measure of large myelinated nerve fiber function) [63•]. Regardless of clinical manifestations, patients with IGT and small-fiber neuropathy had IENF loss that could be reversed with a 1-year diet and exercise intervention program [55••]. Similarly, a study of skin biopsies in diabetic patients showed a correlation between sweat gland nerve fiber density, neuropathic symptoms, neurological deficits, and sweat production [59]. Rapid screening of autonomic or neurological function, therefore, may result in early detection of IGT and metabolic syndrome, early intervention, and reduced morbidity and mortality. Initial studies using SFT for IGT and diabetes screening have shown promising results. A study of SUDOSCAN in 90 diabetic subjects and 142 healthy controls demonstrated that diabetic subjects had significantly lower ESC than did controls (56±1.4 vs. 78±0.7 μS, p<.001) [87], and the sensitivity, specificity, and reproducibility of SUDOSCAN, as reviewed above, were shown to discriminate sudomotor dysfunction between diabetic and control subjects well enough to be applicable in the clinical setting [84]. A second study followed 69 Indian subjects with a normal oral glucose tolerance test but at risk for diabetes longitudinally for the development of diabetes or IGT. After 8 months, 11 and 5 subjects had developed IGT and diabetes, respectively. SUDOSCAN had a sensitivity of 77 % for early detection of IGT and diabetes, while fasting plasma glucose and HbA1c had sensitivities of 14 % and 66 %, respectively [83]. In a parallel study of 212 Chinese subjects at risk of diabetes, SUDOSCAN had an 88 % sensitivity to detect diabetes, 78 % for IGT, and 82 % for normal glucose tolerance (NGT) with metabolic syndrome [87]. A group of 193 healthy German subjects at risk for diabetes were similarly screened with SUDOSCAN: 6 subjects newly diagnosed with diabetes and 30 of 31 subjects with IGT were correctly detected with SUDOSCAN. A longitudinal study of these subjects is ongoing [87]. A large study of 212 Indian subjects at risk for diabetes compared OGTT, HbA1c, lipid panel, and SUDOSCAN for the identification of diabetes, IGT, or NGT with metabolic syndrome. SUDOSCAN had a 75 % sensitivity to detect diabetes, 70 % for IGT, and 84 % for NGT with metabolic syndrome [83].

Because other methods of SFT are much more technically demanding, large population-based studies of their use in the diagnosis and follow-up of diabetes, IGT, and metabolic syndrome have not been completed.

Therapeutic and Interventional Uses of SFT

With the worldwide epidemic of diabetes that we are currently facing, there are ample opportunities for SFT to play a role in changing the course of this disease. The 2012 ADA/EASD guidelines still recommend HbA1c, fasting plasma glucose, or a 2-h 75-g oral glucose tolerance test for diabetes screening; yet, in large outreach screening programs, SFT using SUDOSCAN may be more practical, sensitive, and specific, as reviewed above. For a newly diagnosed type 2 diabetes patient, the ADA’s only recommendation for neuropathy assessment involves testing for proprioception, vibration, reflexes, and monofilament; as for CAN screening, the ADA stresses eliciting a history of symptoms (including sudomotor dysfunction symptoms) and measuring orthostatic blood pressure “when indicated” [88]. However, as was shown above, SFT can be rapidly incorporated into the initial evaluation of a diabetic patient and offer significant insight into his or her risk for autonomic and neuropathic complications.

Beyond its potential for diabetes screening, SFT may play an important role in following patients’ response to clinical intervention or investigational therapies. A large study was recently completed in Finland using SUDOSCAN to assess cardio-metabolic disease risk status and its change in response to lifestyle intervention. Five hundred thirty-seven women and 113 men underwent a CV risk evaluation (including weight, waist circumference, body fat, and VO₂ max) and ESC measurement at baseline. Those with the highest CV risk were invited to participate in a 12-month physical activity program. For the 154 women with the lowest fitness level at baseline, a statistically significant change in waist circumference, weight, body fat percentage, VO₂ max, hand and foot ESC, and SUDOSCAN risk score was observed at 12 months, as compared with baseline. The increase in VO₂ max and ESC were highest in subjects with the highest weekly activity level. Correlation between SUDOSCAN risk score and VO₂ max
was $r = -0.57, p < 0.0001$ for women and $r = -0.48, p < 0.0001$ for men. SUDOSCAN risk scores were highly reproducible whether measured before or after exercise [89]. Although larger studies that include more men are required to confirm these results, the outcome of this program suggests not only that lifestyle intervention using moderate physical activity can have a significant impact on CV risk, but also that a simple tool like SUDOSCAN—rather than the cumbersome VO$_2$ max—can be used in worksite intervention programs to assess and monitor change in CV risk.

Another important role for SFT may be in following poorly controlled diabetes subjects during alteration of their treatment regimen. Gibbons and Freeman recently described the course of treatment-induced diabetic neuropathy occurring with intensive glycemic control. Diabetic patients undergoing rapid lowering of their HbA1c may, rarely, develop acute severe neuropathic pain associated with autonomic dysfunction and microvascular complications (in particular, diabetic retinopathy). After 18 months of ongoing glycemic control, however, pain, autonomic function, and IENF density had improved substantially [90]. Calvert et al. used SUDOSCAN to follow 52 patients with type 1 diabetes and 115 patients with type 2 diabetes clinically over approximately 360 days. The researchers found that after 360 days, ESC in the hands and feet decreased slightly from baseline in type 2 diabetes patients not receiving insulin, while a slight increase in ESC (i.e., improvement in sudomotor function) occurred in type 2 diabetes patients receiving insulin ($-3.8 \pm 9.7$ vs. $1.0 \pm 9.7$ μS, $p = 0.02$ for the hands and $-2.2 \pm 7.5$ vs. $4.1 \pm 8.8$ μS $p < 0.001$ for the feet). Importantly, the two groups did not experience any significant change in HbA1c that would explain or correlate with the observed change in ESC [91]. This study hints at a role for insulin therapy in the evolution of diabetic neurological complications and should encourage further research into evaluating the neurological benefits of various diabetic therapies.

With the substantial number of diabetes patients who need intensification of treatment every year, clinicians should

### Table 2 Comparison of the advantages, disadvantages and research and clinical uses of different methods for sudorimetry

<table>
<thead>
<tr>
<th>Sudorimetry Methods</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
<th>Research Use</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermoregulatory sweat testing (TST) [43, 57]</td>
<td>Whole body assessment; central and peripheral sudomotor fibers assessed</td>
<td>Time and technology intensive; patient prep required; specialized interpretation; low sensitivity, rises to 93 % when combined with QSART</td>
<td>Expensive</td>
<td>Yes</td>
<td>Rarely—lack of availability and cost</td>
</tr>
<tr>
<td>Quantitative sudomotor axon reflex testing (QSART) [97•]</td>
<td>Relatively reproducible; sensitivity, 75 %-90 %, specificity, &gt;90 %</td>
<td>Requires patient prep and trained technician; time consuming</td>
<td>Expensive</td>
<td>Yes</td>
<td>Yes, because most widely available method to date</td>
</tr>
<tr>
<td>Silicone impressions</td>
<td>Simple and relatively quick, quantitative, sensitive</td>
<td>Prone to artifacts</td>
<td>Cheap</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sympathetic skin response (SSR)</td>
<td>Simple; central and peripheral fibers assessed</td>
<td>Surrogate measure of sudomotor function; poor sensitivity in mild dysfunction; low specificity; no population norm; habituation</td>
<td>Cheap</td>
<td>Yes, but restricted to specialized research institutes</td>
<td>No</td>
</tr>
<tr>
<td>Acetylcholine sweat–spot test</td>
<td>Simple and relatively quick</td>
<td>Painful injection; other applications (e.g., heat) more commonly used</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Quantitative direct and indirect axon reflex testing (QDIRT) [78]</td>
<td>Simple and moderately quick, noninvasive, quantitative</td>
<td>Results affected by environmental and patient factors; no normative values</td>
<td>Moderate</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Neuropad [81, 98]</td>
<td>Simple, rapid, objective, sensitivity 57.8 %-97.8 %</td>
<td>Not quantitative, specificity 17.3 %-96.4 %, normative cut-point not defined</td>
<td>Cheap</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Sweat gland nerve fiber density (SNGNFD) [27]</td>
<td>Quantitative, objective; new index SGII under study; area of nerve fibers normalized to area of a sweat gland</td>
<td>Invasive and labor intensive</td>
<td>Expensive</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>SUDOSCAN [84] Parson, 2012 [99]</td>
<td>Quantitative, objective, reproducible, simple, quick, sensitivity 75 %-80 %, specificity 95 %-100 %</td>
<td>No quantitation against other sudorimetry methods (e.g., QSART)</td>
<td>Cheap</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
routinely have access to a rapid outpatient SFT method to monitor autonomic function throughout the course of treatment if severe complications of autonomic dysfunction—even sudden death—are to be avoided.

SFT and Medical Areas of Interest

Neuropathy is a common complication in patients with renal failure, often manifesting as a peripheral polyneuropathy and autonomic dysfunction. Neuropathy is present in up to 65% of patients starting dialysis, while autonomic neuropathy may occur in 50% of patients on dialysis. Although neuropathy may improve with dialysis, it remains associated with worse outcomes in chronic kidney disease [92]. Another important finding is that autonomic neuropathy can improve with renal transplantation [93]. The mechanism of uremic neuropathy remains unclear, and its relationship with the level of kidney function has not been fully elucidated. A number of questions remain. Should the presence or progression of autonomic neuropathy in renal failure trigger dialysis onset or a change in therapy or diet? Does dialysis improve peripheral and/or autonomic neuropathy? What treatments work best in the setting of renal failure to improve neuropathy? What test(s) should be used to diagnose and monitor neuropathy in renal failure patients? There may, in fact, be a role for SFT in renal failure: A small study was conducted in Chinese diabetic patients to detect kidney disease using SUDOSCAN. SUDOSCAN scores, a measure of ESC, were highly correlated with log values of eGFR ($r=.67$, $p<.0001$) [94]. In a study of 167 German diabetic patients, the 20 subjects with nephropathy (MDRD<60 ml/min/1.73 m$^2$) had lower hand and foot ESC than did patients without nephropathy ($63±18$ vs. $72±15$ $p=.07$ and $73±16$ vs. $82±11$ $p=.009$, respectively) [91].

With the advent of antiretroviral therapy (ART), the life expectancy and quality of life of HIV-positive individuals has greatly improved. Simultaneously, however, these individuals may be plagued with small-fiber peripheral neuropathy and autonomic dysfunction. Autonomic dysfunction is associated with a longer duration of HIV infection and has been shown to persist despite treatment with ART [95]. Small-fiber neuropathy is thought to be induced by ART, may be diagnosed late in its course, and is often irreversible and difficult to treat. Very little research has focused on early screening for autonomic and small-fiber neuropathy in the HIV population in order to minimize morbidity. One small study of HIV-positive subjects used QSART and the Utah Early Neuropathy Scale (UENS)—both small-fiber-sensitive scales—to distinguish between subjects with neuropathy and those without. Median sweat volume was significantly lower in neuropathy subjects than in nonneuropathy subjects, and all elements of the UENS were higher in neuropathy subjects than in nonneuropathy subjects [96]. This study should encourage further large-scale research and clinical use of SFT in the setting of HIV disease as a tool for early neuropathy screening.

**Conclusion**

Thermoregulatory function is dependent upon SKBF to the glabrous and hairy skin, as well as the nerve fiber innervation of the sweat glands and the density of sweat glands in the human body. Innumerable studies now show that there is a marked defect in blood flow of both endothelial-derived and direct vasodilatory mechanisms in diabetes, as well as in prediabetes, IGT, and the metabolic syndrome. Interestingly, a greater impact on neuropeptidergic and prostaglandin-mediated vasodilation of hairy skin is found in diabetes as well as prediabetes, while sympathetically mediated vasodilation—the major regulator of SKBF in glabrous skin—remains relatively unaffected until there is advanced disease. In contrast, disturbances in thermoregulatory sweating and sympathetic cholinergic-mediated sweating occur early in the evolution of prediabetes to diabetes and may even herald the development of diabetes.

The body’s sweat glands are intimately linked to the ANS via sympathetic C fibers. We now have the technological power to take advantage of this physiological arrangement to better understand, monitor, and treat disorders of small nerve fibers and the ANS. In particular, we should use all means available to aggressively screen for cardiac and peripheral somatic and autonomic neuropathy; any reduction in the morbidity and mortality of CAN by recognition and preventive treatment is likely to reduce morbidity and mortality. Newer methods of SFT are rapid, noninvasive, not technically demanding, and accessible to the outpatient clinic. Table 2 compares the advantages, disadvantages, research, and clinical uses of different methods for sudomimetry. In particular, SUDOSCAN, an FDA-approved device, has excellent potential in the clinical setting for assessing sudomotor function given its ease of use. The incorporation of SUDOSCAN into routine practice would streamline how patients are currently screened for new onset and follow-up of chronic diseases. Other methods of SFT, such as Neuropad, QSART, QDIRT, silicone impressions, SSR, and acetylcholine sweat-spot, are underutilized, since it is generally not feasible to perform them in a routine setting and they may not be fully sensitive for diagnosing particularities of autonomic dysfunction diseases. SUDOSCAN is reproducible and, as previously noted, proven in research studies to be an accurate measure of small- and large-nerve-fiber disorders. Whether the potential applications are screening for diabetes, following poorly controlled diabetes subjects during alteration of their
treatment regimen, or simply monitoring somatic and autonomic function throughout the course of treatment, SUDOSCAN can be an invaluable tool for today’s clinicians.

Conflict of Interest  Aaron I. Vinik has received grant support from Impeto-Medical for a funded study on “sudoscan”; has received support for travel to meetings for the study or otherwise from Impeto-Medical for investigator meetings; has been a consultant for Merck Pharmaceuticals, Pfizer Pharmaceuticals, and ISIS Pharmaceuticals; and has received grant support from Pfizer, ViroMed, and Sanofi-Aventis.

Marie Nevoret has been a consultant for Impeto-Medical.

Carolina Casellini declares that she has no conflict of interest.

Henri Parson declares that he has no conflict of interest.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance


