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

Abstract
Sudomotor dysfunction is a common finding, and one of the earliest detectable abnormalities, in a number of peripheral and autonomic neuropathies. However, clinicians can attest to the ongoing difficulty in diagnosing dysautonomia without the proper tools. Sudomotor function testing (SFT) as assessed with Quantitative Sudomotor Assessment Reflex Test (QSART) correlates well with Intraepidermal Nerve Fiber Density (IENFD) from skin biopsies, which is considered one of the most objective quantitative measures of peripheral neuropathy. Similarly, Sweat Gland Nerve Fiber Density (SGNFD) correlates with scores used to assess peripheral neuropathy such as Neuropathy Impairment Score in the Lower Limb (NIS-LL) and Michigan Neuropathy Screening Instrument (MNSI). Sweat gland sympathetic nerve fibers are an integral part of the Autonomic Nervous System (ANS), a system in which the predominant dysfunction observed is Cardiac Autonomic Neuropathy (CAN) — this condition is recognized as a serious complication of diabetes, with a prevalence from 2.5 to 50% in patients with this disease. CAN persists in being an implication of the cause for an approximately 5-fold risk of mortality in such patients. Today, standardized implementation of cardiac autonomic reflex tests is used to identify peripheral and autonomic neuropathies. While these assessments are non-invasive and safe to perform, they have certain limitations. These assessments are influenced by caffeine, tobacco and exercise, a fact which must be taken into account when interpreting the results.

Current methodologies for sudomotor function testing, i.e., QSART, Thermal Sensory Testing (TST) and Sympathetic Skin Response (SSR) used in standard practice remain underutilized. They cannot generally be performed in routine clinical setting and may not be fully sensitive for diagnosing the particularities of autonomic dysfunction diseases. Compared to these “gold standards,” SUDOSCAN, an FDA-cleared device, proves to be an excellent and reliable method to assess sudomotor function testing. SUDOSCAN is accessible, non-invasive, requires less than 3 minutes to conduct from start to finish, provides immediate results and requires no patient preparation. It has the ability to detect early onset abnormalities and evaluate treatment efficacy of chronic diseases. Utilizing SUDOSCAN as a clinical diagnostic tool allows dysautonomia to be better identified and treated in today’s clinical practice.

Introduction
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 neuropathy1. The various techniques of sudomotor function testing (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.

This article reviews the sweat gland anatomy and physiology, its relationship to small nerve fibers, SFT techniques, and the current and prospective clinical applications of SFT.

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. 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.

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. 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. 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.

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. This reflex is used as the mechanism for SFT in a number of tests (QSART, for example).

Particularities of the autonomic sympathetic nerve fibers which 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 but could be evaluated early in the course through the assessment of sudomotor function.
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 (CFTR) gene mutations in an individual. 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.

Nonetheless, critical new applications are now being recognized for sudomotor function testing – both in the clinical and the 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 sudomotor function testing to assess dysfunction of the peripheral and autonomic (sympathetic) nervous systems. Sweat gland testing holds a number of advantages compared to 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. Sudomotor function testing as assessed with QSART correlates well with intraepidermal nerve fiber density (IENFD) from skin biopsies, which is considered one of the most objective quantitative measures of peripheral neuropathy. 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. Similarly, sweat gland nerve fiber density (SGNFD) correlates with Neuropathy Impairment Score in the Lower Limb (NIS-LL) and Michigan Neuropathy Screening Instrument (MNSI). 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, though 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. 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 system, allowing for earlier intervention and a reduction in consequent morbidity and mortality. In addition, as 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. They may occur secondary to diabetes, glucose intolerance, toxins (e.g. alcohol), HIV, connective tissue disease, sarcoidosis,
drugs (antiretrovirals, chemotherapeutic agents), and idiopathy. In diabetes, sensorimotor polyneuropathy (DSPN) is the most common type, affecting about 25% of patients with diabetes in the community. 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 paresthesias and pain. The course of DSPN is insidious, though, and up to 50% of patients with neuropathy may be asymptomatic – 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 risk factors. Furthermore, DSPN has been shown to be statistically associated with retinopathy, and nephropathy, and may occur concurrently with autonomic neuropathy. In diabetic peripheral neuropathy, sudomotor dysfunction may in itself result in dryness of the foot skin and has been associated with foot ulceration.

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’. 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. Considering that large nerve fiber tests (such as nerve conduction tests) may remain normal until neuropathy is quite advanced, sudomotor function testing – which measures small nerve fiber function – holds a temporal advantage in the diagnosis of peripheral polyneuropathies.

**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 autonomic nervous system (ANS). The ANS is the primary extrinsic control mechanism regulating heart rate, blood pressure, and myocardial contractility. Cardiac autonomic neuropathy (CAN) describes a dysfunction of the autonomic nervous system and its regulation of the cardiovascular 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. In the diabetes population, the prevalence of CAN varies from 2.5 to 50%; in the EURODIAB IDDM Complications study, it was calculated to be 36%. CAN is implicated as the cause for an approximately 5-fold risk of mortality in diabetes patients; a large body of evidence demonstrates that CAN is the strongest predictor for mortality in diabetes mellitus, independently of baseline cardiovascular disease (CVD), diabetes duration, traditional CVD risk factors and medications. CAN also results in serious and costly morbidities (silent myocardial infarction, coronary artery disease, stroke, progression of diabetic nephropathy, and perioperative complications).

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 - its diagnosis is frequently delayed or may never occur before the occurrence of a catastrophic event. Today, there are well-established, non-invasive testing methods to detect and monitor CAN, and, because of the large number of affected patients, screening for CAN should be routinely considered. Resting tachycardia (heart rate 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. suggest 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. There may even be a role for more aggressive screening, as subclinical CAN may occur in patients with impaired glucose tolerance, years prior to the development of overt diabetes. Beyond diagnosis, testing for CAN may distinguish between static and progressive disorders, as well as treatment response over time.

Evaluation of CAN must assess the 3 components of the autonomic system: cardiovagal (parasympathetic), adrenergic (sympathetic), and sudomotor (sweating) functions. Kempler suggests using corrected QT interval – a specific, albeit insensitive indicator of autonomic dysfunction - as a screening test to select patients for more extensive CAN evaluation. Standardized testing batteries have been described in a number of consensus statements. 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 cardiovascular autonomic system.

In depth descriptions of the cardiovagal and adrenergic testing methods for CAN can be found elsewhere. Assessment of sudomotor function provides a measure of the sympathetic cholinergic function in the workup of CAN. Though 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. QSART has been found to be the most sensitive physiologic autonomic test in small fiber neuropathy, with a sensitivity of 75 to 90%. Fealey conducted 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.

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

Available techniques include thermoregulatory sweat testing (TST), quantitative sudomotor axon reflex testing (QSART), silicone impressions, sympathetic skin response (SSR), acetylcholine sweat-spot test, quantitative direct and indirect axon reflex testing (QDIRT), and SUDOSCAN. An in-depth review of the details of these techniques has been recently published by Illigens and Gibbons; 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 which has limited availability, patient
preparation, proper interpretation of normal variants, and time.

Quantitative sudomotor axon reflex test (QSART) is currently the most widely available SFT method. Four testing sites are used (forearm, proximal leg, distal leg, and dorsum of the foot). 10% 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 (though there have been inconsistent results),28 has a sensitivity of 75% to 90% for small fiber neuropathies, and often correlates with IENFD.12,6 However, a number of drawbacks have kept QSART from widespread clinical utilization: it can only assess the post-ganglionic sudomotor response; the patient has to be adequately prepared and the test can be time-consuming; the equipment is expensive and specialized; test performance requires a trained technician; and 4 sites on the body must be tested.

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 minutes, 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.

The acetylcholine sweatspot and quantitative direct and indirect axon reflex testing (QDIRT) both measure postganglionic sympathetic sudomotor function using a cholinergic stimulus. For the sweatspot test the skin is initially painted with reagent dye; acetylcholine is then injected intradermally and the resulting sweat droplets can be visually quantified. For QDIRT a cholinergic agent is iontophoresed into the skin, then a reagent dye is applied and pictures are taken over a 7 minute period allowing digital quantification of direct and indirect sweat production. The injection of acetylcholine for sweatspots may be painful and unacceptable to patients. QDIRT is a newer technique and can be quite sensitive to ambient temperature, humidity, and the hydration and caffeine intake of the patient.

Sympathetic skin response (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 CNS degeneration. The source of the skin’s electrical potential is unclear but 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.

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 electrode...
plates, while low voltage DC combinations are applied over a course of 2 minutes as a stress test of the glands’ ability to release chloride ions. The output reading is the 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, i.e. dysfunction of the sympathetic C fibers innervating sweat glands. SUDOSCAN testing is entirely painless, can be conducted in 3 minutes, and requires no special patient or equipment preparation. Test administration and result interpretation also demand no special training. 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 left and right side 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 < 40µS were more than 4 times as likely as patients with ESC ≥ 40µS to have 2 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.

Sensitivity, specificity, and reproducibility of SUDOSCAN were measured among 133 type 2 diabetes patients compared to 41 healthy controls. ESC values had a sensitivity of 75% and a specificity of 100%, with an area under the ROC curve of 0.88 at a threshold of 50%; coefficients of variation in hand and foot measurements were 15 and 7%, respectively. A similar study among 142 French diabetic patients showed that descending foot ESC measurements from 66±17µS to 43±39µS correlated to increasing VPT threshold from <15V to >25V (p=0.001), regardless of blood glucose levels.

**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 (NISS). 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.

Similarly, autonomic neuropathy is most commonly diagnosed when symptoms and clinical signs are quite advanced, i.e. 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. With recent technological advancement in sudomotor function testing 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, sudomotor function testing 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, e.g. as one component of the 10-point composite autonomic scale. 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 cystic fibrosis, newer SFT technology has been demonstrated to be accurate in confirming the diagnosis: SUDO SCAN 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 which were significantly higher in CF patients as compared to healthy adults (75±10µSi vs. 62±13µSi, p<0.0001). 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 SUDO SCAN opens many opportunities for further use in cystic fibrosis: ESC results need to be correlated with sweat chloride concentration; SUDO SCAN 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.

**Peripheral and autonomic neuropathy**

The cardiovascular autonomic reflex tests are the gold standard for clinical autonomic testing. They essentially measure heart rate and blood pressure changes during provocative physiological maneuvers. These tests are non-invasive 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. Sudomotor function testing, and in particular newer techniques such as SUDO SCAN, may allow wider clinical screening for CAN 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; 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. 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 minute SUDO SCAN test were significantly associated with measures of peripheral neuropathy (MNSI, VPT) as well as cardiac sympathetic dysfunction. 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 impaired glucose tolerance (IGT) or metabolic syndrome, years prior to a diagnosis of diabetes mellitus. These patients may be symptomatic or asymptomatic, and have normal or abnormal nerve conduction velocities (a measure of large myelinated nerve fiber function). Regardless of clinical manifestations, patients with impaired glucose tolerance and small fiber neuropathy had IENF loss which could be reversed with a 1-year diet and exercise intervention program. 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. Rapid screening of autonomic or neurological function, therefore, may result in early detection of impaired glucose tolerance and metabolic syndrome, early intervention, and reduced morbidity and mortality. Initial studies using sudomotor function testing 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 controls (56±1.4 versus 78±0.7µS, p<0.001); 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. A second study followed 69 Indian subjects with 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. 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. 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. 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.

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-hour 75g 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.’ However, as shown above, sudomotor function testing 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. 537 women and 113 men underwent a cardiovascular (CV) risk evaluation (including weight, waist circumference, body fat and VO\textsubscript{2} max) and ESC measurement at baseline. Those with the highest CV risk were invited to participate in a 12 months physical activity program. For the 154 women with the lowest fitness level at baseline, a non-statistically significant change in waist circumference, weight, body fat percentage, VO\textsubscript{2} max was observed as hand and foot ESC, and SUDOSCAN risk score was observed with statistically significant change at 12 months compared to baseline. The increase in VO\textsubscript{2} max and ESC were highest in subjects with the highest weekly activity level. Correlation between SUDOSCAN risk score and VO\textsubscript{2} max was \( r = -0.57, p<0.0001 \) for women and -0.48, \( p<0.0001 \) for men. SUDOSCAN risk scores were highly reproducible whether measured before or after exercise\textsuperscript{35}. Though 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\textsubscript{2} max - can be used in worksite intervention programs to assess and monitor change in CV risk.

Another important role for sudomotor function testing 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 (GibbonsFreemansan)\textsuperscript{36}. Schwartz 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. and improvement in sudomotor function) occurred in type 2 diabetes patients receiving insulin (-3.8±9.7 vs. 1.0±9.7\( \mu \)S p=0.02 for the hands and -2.2±7.5 vs. 4.1±8.8\( \mu \)S p<0.001 for the feet). Importantly, the 2 groups did not experience any significant change in HbA1c which would explain or correlate with the observed change in ESC. 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 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. Though neuropathy may improve with dialysis, it remains associated with worse outcomes in chronic kidney disease\textsuperscript{38}. Another important finding is that autonomic neuropathy can improve with renal transplantation\textsuperscript{39}. 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=0.67, p<0.0001)\(^4\). In a study of 167 German diabetic patients, the 20 subjects with nephropathy (MDRD<60ml/mn/1.73m\(^2\)) had lower hand and foot ESC than patients without nephropathy (63±18 vs. 72±15 p=0.07 and 73±16 vs. 82±11 p=0.009, respectively)\(^4\).

Uremic neuropathy is a prevalent morbidity and sudomotor function testing may have a role to play not only in the research arena but as an agile screening and monitoring tool in clinical practice.

With the advent of anti-retroviral 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\(^4\). 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 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 compared to non-neuropathy subjects, and all elements of the UENS were higher in neuropathy subjects compared to non-neuropathy subjects\(^4\). This study should encourage further large scale research and clinical use of sudomotor function testing in the setting of HIV disease as a tool for early neuropathy screening.

**Conclusion**

The body’s sweat glands are intimately linked to the autonomic nervous system 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 autonomic nervous system. In particular, we should use all means available to aggressively screen for cardiac autonomic neuropathy, whether stemming from underlying diabetes, renal failure, HIV or another disorder; any reduction in the morbidity and mortality of CAN would greatly improve outcomes in these chronic conditions. Newer methods of sudomotor function testing are rapid, non-invasive, not technically demanding, and accessible to the outpatient clinic.

SUDOSCAN, a 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 QSART, QDIRT, silicone impressions, SSR and acetylcholine sweat-spot are under utilized as 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 nerve fiber disorders and autonomic dysfunction. Whether the potential applications are screening for diabetes, following poorly controlled diabetes subjects during alteration of their treatment regimen, or simply monitoring autonomic function throughout the course of treatment, SUDOSCAN can be an invaluable tool for today’s clinicians. The ability to diagnose early and maintain the health of patients with respect to autonomic dysfunction would prove to be of great benefit in today’s preventive care approach.
References


Comparison With VO₂ Max In A Follow-Up Study. accepted for publishing.


