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REVIEW

Electrochemical skin conductance: a systematic review

Peter Novak[1]

Abstract

Purpose Currently available techniques for the evaluation of small fiber neuropathy and related sudomotor function remain suboptimal. Electrochemical skin conductance (ESC) has recently been introduced as a simple noninvasive and fast method for the detection of sudomotor dysfunction. The purpose of this review is to synthesize and appraise research using ESC measurements for sudomotor evaluation in adults.
Methods Electronic databases including MEDLINE and Google Scholar were searched (up to March 13, 2017). The search strategy included the following terms: "electrochemical skin conductance," "Sudoscan," and "EZSCAN." Evidence was graded according to defined quality indicators including (1) level of evidence; (2) use of established tests as reference tests (e.g., quantitative sudomotor axon test [QSART], sympathetic skin responses [SSR], thermoregulatory sweat test [TST], and skin biopsies to assess sudomotor and epidermal small fibers); (3) use of consecutive/nonconsecutive subjects; and (4) study design (prospective/retrospective).
Results A total of 24 studies met the inclusion criteria. These were classified into preclinical, normative, comparative/diagnostic, or interventional. ESC measurement properties, diagnostic accuracy, and similarities to and differences from established tests were examined.
Conclusions ESC measurements expand the arsenal of available tests for the evaluation of sudomotor dysfunction. The advantages and disadvantages of ESC versus established tests for evaluating sudomotor/small fiber function reviewed herein should be used as evidence to inform future guidelines on the assessment of sudomotor function.

Keywords Electrochemical skin conductance · ESC · Sudoscan · Small fiber neuropathy · Dysautonomia · Autonomic

Introduction

Small nerve fibers are thinly myelinated Aδ fibers and unmyelinated C fibers, which are further classified as autonomic (efferent) or sensory/somatic (afferent). Their dysfunction (i.e., small fiber neuropathy [SFN]) can result in autonomic symptoms, sensory symptoms, or a combination of both. SFN with mixed involvement of both sensory and autonomic fibers is the most common form, affecting millions of individuals worldwide and contributing significantly to morbidity [1–6]. SFN can be further classified into idiopathic or secondary. Among the secondary causes, cardiovascular autonomic neuropathy (CAN) caused by diabetes mellitus (DM) is a common cause of SFN [5]. CAN is present in up to 90% of patients with type 1 and 20–73% of patients with type 2 diabetes mellitus [5], depending on the diagnostic test. Medical history and physical examination, although important, are usually insufficient for establishing a diagnosis of SFN with a high level of certainty or for determining its severity. Therefore, patients with suspected SFN with autonomic dysfunction should undergo ancillary diagnostic testing to confirm the diagnosis.

Established objective autonomic function tests endorsed by the American Autonomic Society (AAS) for the evaluation of sudomotor function include the quantitative sudomotor axon test (QSART), the sympathetic

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skin response (SSR), and the thermoregulatory sweat test (TST) [7]. When cardiovascular autonomic failure is suspected in addition to sudomotor dysfunction, cardiovascular autonomic testing (including Valsalva maneuver, heart rate variability during paced deep breathing, and tilt-table test with continuous blood pressure readings with plethysmography) is recommended.

Additional methods for evaluating SFN include skin biopsy for the quantification of epidermal nerve fiber density (ENFD) [6] and sudomotor (sweat gland) nerve fiber density (SGNFD) [8]. ENFD is the standard test for evaluation of SFN with high diagnostic accuracy and is recommended by the European Federation of Neurological Societies (EFNS) [3]. The diagnostic accuracy of SGNFD, however, has yet to be established. A number of challenges remain in evaluating the autonomic nervous system. The main difficulty arises from the fact that most functional tests quantify the end-organ effect of the autonomic input but not the autonomic nerve function per se.

Electrochemical skin conductance (ESC) was recently introduced as a simple electrophysiological method for the functional evaluation of sweat glands and related sudomotor/small fiber dysfunction [9–12]. The rationale and methodology involving ESC is explained in detail in the "Results" section. Similar to the majority of functional autonomic tests, ESC measures end-organ responses as a surrogate marker of autonomic nerve function. There are two types of human sweat glands: eccrine and apocrine. Eccrine sweat glands cover most of the skin; they produce a clear sweat composed primarily of water and sodium chloride, and they play a major role in thermoregulation. Apocrine sweat glands are concentrated in the scalp, armpits, and groin; they produce a dense sweat released in the canals of hair follicles, and they do not participate significantly in thermoregulation. Postganglionic sympathetic cholinergic non-myelinated C fibers innervate the periglandular tissue of the eccrine sweat glands [13]. A minority of these fibers are adrenergic, but their role in thermoregulation is questionable. ESC measurements assess eccrine gland sweat production.

In this work, we performed a systematic literature review of studies using ESC. Here, we summarize their limitations, potential clinical applications, advantages and disadvantages, and comparison with other well-established tests for evaluating sudomotor function. Specifically, this review addresses two questions:

1. Can ESC provide accurate measurements of sympathetic sudomotor (cholinergic) function?
2. Do ESC results correlate with other established tests of sudomotor function or sweat gland morphology?

Methods

Literature search strategy

A search of the PubMed and Google Scholar (scholar.google.com) databases was performed for the period up to March 13, 2017, using the following search terms: "electrochemical skin conductance" [All Fields] OR "Sudoscan" [All Fields] OR "EZSCAN" [All Fields]. The search yielded 47 entries. Only peer-reviewed scientific articles were considered; review articles or studies with overlapping results were excluded.

Quality ratings

In order to quantify the quality of each publication, the level of evidence (Table 1) [14] and several quality indicators were extracted. Quality indicators included:

a. Comparison with well-established sudomotor tests (QSART, TST, or SSR).
b. Prospective versus retrospective study: if the study was not explicitly described in the methods section as prospective, it was considered retrospective, unless it was obvious from the methods that the study was prospective.
c. Consecutive versus non-consecutive inclusion of patients: if the study did not specify whether consecutive patients were included, non-consecutive inclusion was assumed.
d. Performance of skin biopsy for assessment of small fiber density using a methodology defined by the EFNS [3].
e. Performance of standardized cardiovascular autonomic testing. Established autonomic testing was defined by AAS recommendations [7] for autonomic screening, and included heart rate variability during paced deep breathing, tilt-table test, and Valsalva maneuver, and one of the following: QSART, TST or SSR.

Table 1 Definition of quality level

Level 1	Testing of previously developed diagnostic criteria, with enrollment of consecutive patients, with consistently applied reference standard and blinding
Level 2	Development of diagnostic criteria, with enrollment of consecutive patients, with consistently applied reference standard and blinding
Level 3	Non-consecutive patients No consistently applied reference standard
Level 4	Poor or non-independent reference standard
Level 5	Mechanism-based reasoning

f. For interventional studies, whether the intervention was randomized and the patients/investigators were blinded to the intervention [14].

Results

Twenty-two studies fulfilled the inclusion criteria. Figure 1 shows a PRISMA flow diagram [15]. The selected publications included preclinical/mechanism-of-action studies, normative diagnostic or correlation studies (using a reference test), and interventional studies.

Preclinical and mechanism-of-action studies

Two studies analyzing preclinical data were retrieved. The measurement of ESC is an active electrophysiological method based on two physical principles [9, 10, 12]: (1) low-voltage electrical activation of sweat glands and (2) reverse iontophoresis to capture the flow of chloride ions produced by activated sweat glands. ESC measures the flow of chloride ions induced by electric current. According to a theoretical model, electric current directly stimulates the sudomotor fibers, innervating the sweat glands. Subsequently, the glands produce sweat, which is composed of chloride ions. The chloride ions are consumed at the anode, mimicking the corrosion process using principles of reverse electrophoresis. In direct iontophoresis, ions move in a medium driven by an electric current [16]. In reverse iontophoresis, also called electro-osmotic flow, the molecules are extracted from the medium. In the case of ESC, subepidermal chloride ions are moved to the skin surface. Human skin has relatively high electrical capacitance due to its dense lipid layers, and therefore the ions cannot penetrate the stratum corneum at low voltage [12, 17]. However, ions driven by electric current can move in an electric field via sweat duct pores. In vitro electrochemical studies [18] evaluating nickel and stainless steel electrode behavior in sweat-mimicking solutions showed that the concentration of chloride had a strong influence on the anodic potential. The chloride ion flow produced by sweat glands is proportional to the level of stimulus and sweat gland function. Since the stimulus is electrical, it is possible to exactly define the intensity of the stimulation level, which may be a key factor in reproducibility.

During ESC measurement, subjects place both palms and soles on large-area stainless-steel electrodes. An incremental low direct voltage (< 4 V) is applied for 15 s. The voltage applied on skin electrodes generates a current between the anode and the cathode that is measured. For example, the right-foot electrode is used as an anode, and voltage of 1 V is applied for 1 s. This induces voltage on the cathode, i.e., the left-foot electrode, and a current travels through the body towards the cathode. The voltage occurring on the cathode is measured using a voltmeter, and the current between the electrodes is measured using a Wheatstone bridge. The voltage applied on the anode is then increased to 1.2 V over 1 s, and a new measurement is performed. The voltage continues to be increased in increments of 0.2 V per second until a maximum voltage of 3.8 V is reached (15 steps in all). The same 15 incremental increases in voltage are applied on the left-foot electrode used as anode, while the right-foot electrode is used as cathode. Finally, the same 15 steps are applied twice on the hand electrodes, with each electrode used alternately as an anode or a cathode.

Fig. 1 A flow chart showing data collection process (PRISMA flow diagram)
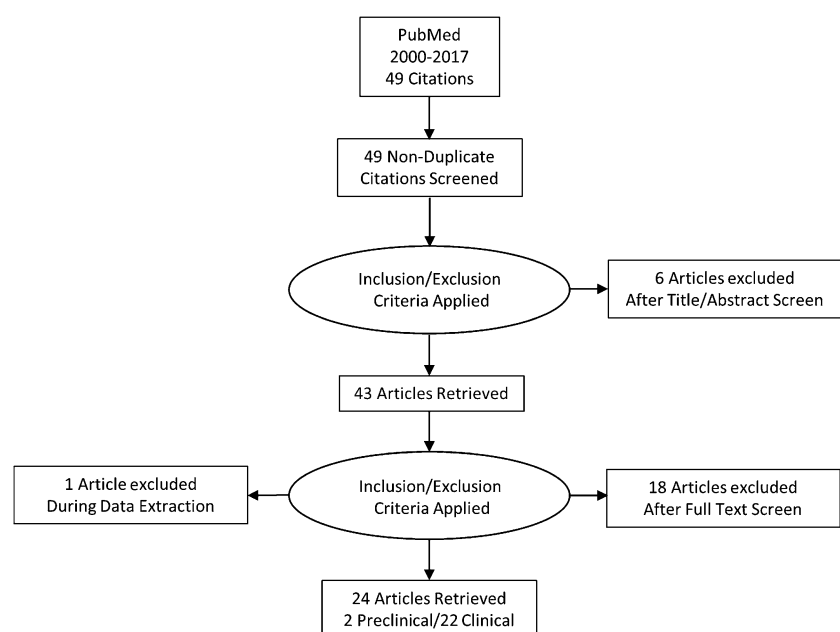
The ESC is calculated from the generated current, which is expressed as follows: (1) current as a function of the anodic potential (so-called E); (2) current as a function of the cathodic potential after applying an incremental voltage at the anode (so-called V); and (3) current as a function of $U = E + V$. Quantitative results are expressed as ESC, i.e., a ratio of the current generated and the direct voltage stimulus in microsiemens (μS). Two ESC values are usually provided separately for the average of the two hands and the two feet.

Clinical studies

Table 2 shows a summary of the clinical studies reviewed, along with their quality assessment. Only one study had level-1 quality (higher quality standard), and only one had level-2 quality. The others were all of level-3 or worse quality.

Studies describing the properties of ESC measurements

Safety and tolerability   The measurement of ESC is consistently safe and tolerable, as no discomfort or adverse events were reported in 1376 tests performed on healthy participants [19].

Symmetry   There were no differences between the left and right sides, with a high correlation of ESC values between the right and left hands ($r = 0.96$, $p < 0.0001$) and the right and left feet ($r = 0.97$, $p < 0.0001$) among 1350 healthy participants [19].

Ethnicity, body mass index, sex, and age effect   ESC values appear to be lower in African American, Indian, and Chinese subjects than in whites [19]. There was no significant effect of body mass index on ESC measurements [19]. No differences were observed in ESC measured in hands and feet between men and women [9, 19]. In a study evaluating 1350 participants, ESC in the hands and feet decreased significantly with increasing age ($R = -0.17$, $p < 0.0001$; feet: $R = –0.19$, $p < 0.0001$) [19]. Thus, studies using ESC should include age as a covariate.

Reproducibility   When ESC measurements were performed in the same patient twice during the same day, the coefficients of variation were 7% for the hands and 5% for the feet of patients with cardiovascular risk, and 15% and 7%, respectively, for the hands and feet of patients with diabetes [9].

Diagnostic, comparative, or association studies

These studies were designed to study ESC measurements in different disorders, all characterized by defective sudomotor function. Some studies also determined potential associations with established markers of autonomic, sensory, or motor dysfunction.

Cystic fibrosis

Cystic fibrosis is a genetic disorder characterized by defective electrolyte transport associated with increased sweat chloride concentration [20]. ESC was measured in 41 adult patients with classical cystic fibrosis and 20 healthy controls [12]. ESC on the hands and feet was increased in patients with cystic fibrosis compared to controls (feet: 75 ± 10 vs. 62 ± 13 μS; hands: 73 ± 14 vs. 61 ± 15 μS; $p < 0.01$ in both cases). This is consistent with the mechanism of action of the ESC technique, which is based on chloride iontophoresis.

Diabetic neuropathy

Most studies are based on the premise that sudomotor dysfunction occurs due to chronic hyperglycemia and related metabolic perturbations in patients with diabetes or abnormal glucose metabolism. In a study performed in China, Zhu et al. [21] used ESC as an early biomarker for metabolic syndrome. The study included 1078 participants, 567 of whom had metabolic syndrome. Participants with metabolic syndrome had reduced ESC (70.6 ± 13 μS [cardiac risk score 20–29] and 63.2 ± 16.6 μS [cardiac risk score ≥ 30]) compared to controls (78.1 ± 10.1 μS, $p < 0.0001$).

A study by Freedman et al. [22] evaluated 205 African Americans with type 2 diabetes mellitus, 93 African American non-diabetic controls, 185 European Americans with type 2 diabetes mellitus, and 73 European American non-diabetic controls. The authors found that ESC was lower in subjects with type 2 diabetes mellitus and also in African Americans. After adjusting for age, sex, BMI, and HbA1c, ESC decreased with decreasing renal function (estimated glomerular filtration rate [eGFR]) in African Americans with type 2 diabetes mellitus. Another study [23] examined the relationship between ESC and other parameters of renal function (eGFR and albumin-to-creatinine ratio in urine) in 202 European Americans and 181 African Americans with type 2 diabetes mellitus. Specific attention was paid to patients with diabetic kidney disease, as defined by an eGFR below 60/ml/min/1.73 m^2. ESC decreased with decreasing renal function in both ethnic groups, but was lower in patients with type 2 than type 1 diabetes mellitus [24]. Another study including 2833 Chinese adults with type 2 diabetes mellitus showed that lower ESC scores were associated with chronic kidney disease, with moderate sensitivity (76.7%) and specificity (63.4%) [25]. A cross-sectional study including 36 patients with type 2 diabetes mellitus and coronary artery disease and 20 age- and sex-matched controls showed that ESC was significantly lower in patients

Table 2 Summary of the major clinical studies included in this systematic review

Author and year	Disorder	Main reference test	Standardized autonomic testing	Sensitivity/specificity	Sponsor	Skin biopsy	Prospective design	Consecutive enrollment	Quality level	Comments
Hubert et al. 2010 [12]	Cystic fibrosis	CF	–			–	–	–	5	Pilot, proof-of-concept study
Zhu et al. 2016 [21]	Metabolic syndrome	Cardiac risk score	–		Impeto, China Health Promotion	–	–	–	3	Correlation study
Freedman et al. 2014 [22]	DM	DKD	–		Impeto, NIH grants	–	–	–	3	Association study
Freedman et al. 2015 [23]	DM	DKD	–		Impeto, NIH grants	–	–	–	3	Association study
Chen et al. 2015[29]	IGT, DM	IGT (fasting glucose), DM (fasting glucose)	–	82/62 53/59	Not given	–	–	–	3	Diagnostic study
Luk et al. 2015 [25]	DM	DKD	–	76.7/63.4	Impeto	–	–	+	3	Diagnostic accuracy study
Mao et al. 2016 [31]	DM	DN (NSS/NDS)	–		National Natural Science Foundation of China	–	–	–	4	Detection of asymptomatic DN
Calvet et al. 2013 [24]	SFN	Diabetes	–	83/63		–	–	–	4	Observational comparative study
Casellini et al. 2013 [30]	DM	NIS-LL	–	78/92	Impeto	–	–	–	3	Diagnostic study
Smith et al. 2014 [38]	DSP (DM and non-DM)	UENS	–	77/67	Impeto, NIH, ADA	+	–	–	3	Diagnostic study
Novak 2016 [39]	SFN (DM and non-DM)	SGNFD, ENFD	+	–	Impeto provided the device	+	+	+	1	Correlation study, blinded
Chahal et al. 2017 [26]	DM	PAD	–		Not given	–	+	+	3	Association study
Syngle et al. 2015 [42]	RA, AS	ESC, CAT-E	–	N/A		–	+	+	2	Interventional study, ESC improved
Ramachandran et al. 2010 [28]	IGT, DM, Metabolic syndrome	IGT DM Metabolic syndrome	–	75/ 70/ 84/		–			3	Diagnostic study
Mayaudon et al. 2010 [27]	DM	DM	–	75/100	Impeto	–	+	–	3	Diagnostic study
Yajnik et al. 2012 [35]	DM	VPT	–	73/62	Impeto	–	–	–	3	Diagnostic study

Table 2 (continued)

Author and year	Disorder	Main reference test	Standardized autonomic testing	Sensitivity/specificity	Sponsor	Skin biopsy	Prospective design	Consecutive enrollment	Quality level	Comments
Yajnik et al. 2013 [36]	DM	CAN	–	92/49	Impeto	–	–	–	3	Diagnostic study
Sheshan et al. 2016 [34]	DM	DPN (AAN criteria) (NSS/NDS/VPT)	–	67.5/58.9	None	–	–	–	3	Diagnostic study
Ang et al. 2017 [37]	DM	Baseline ESC CAN	–	N/A	NIH, ADA, Impeto	–	+	–	3	Comparative study
Casellini et al. 2016 [43]	Obese subjects with and without DM	Baseline ESC	–	N/A	Impeto	–	+	–	3	Interventional study, non-blinded, non-randomized, ESC improved
Castro et al. 2016 [40]	TTR-FAP	Compound autonomic dysfunction test, sensory symptoms	–	76/85 67/76	Pfizer, Inc.	–	–	–	3	
Selvarajah et al. 2015 [32]	DM	DPN (AAN criteria) CAN	–	88/76 65/80	No specific funding received	–	–	–	3	Diagnostic study

AAN American Academy of Neurology, *ADA* American Diabetes Association, *AS* ankylosing spondylitis, *CAN* cardiac autonomic neuropathy, *CAT-E* cardiovascular reflex tests according to Ewing, *CF* cystic fibrosis, *DM* diabetes mellitus, *DKD* diabetic kidney disease (eGFR < 60 ml/min/1.73 m^2), *DN* diabetic neuropathy, *DPN* diabetic peripheral neuropathy, *DSP* distal symmetric polyneuropathy, *eGFR* estimated glomerular filtration rate, *ENFD* epidermal nerve fiber density, *IGT* impaired glucose tolerance, *NDS* Neuropathy Disability Score, *NIS-LL* Neuropathy Impairment Score-Lower Limbs, *NSS* Neuropathy Symptom Score, *PAD* peripheral artery disease, *RA* rheumatoid arthritis, *SFN* small fiber neuropathy/sudomotor dysfunction, *SGNFD* sweat gland nerve fiber density, *TTR-FAP* transthyretin familial amyloid polyneuropathy, *UENS* Utah Early Neuropathy Scale, *VPT* vibration perception threshold

+, present; -, absent

than in controls, and that lower ESC results were associated with higher C-reactive protein levels, higher HbA1c, and lower ankle-brachial index, a marker of peripheral artery disease [26]. The accuracy and reproducibility of ESC measurements were tested in 133 patients with type 2 diabetes mellitus and 41 controls. The sensitivity and specificity of low ESC measurements (cutoff point of $< 50\%$ of the EZSCAN scale) for the diagnosis of type 2 diabetes mellitus were 75% and 100%, respectively [27]. In a study including Asian Indian subjects [28], low ESC measurements (cutoff point of $< 50\%$ of EZSCAN scale) demonstrated sensitivity of 75% for diagnosing type 2 diabetes mellitus, 70% for diagnosing impaired glucose tolerance, and 84% for detecting metabolic syndrome. A similar study in Chinese subjects found similar sensitivity and low specificity for detecting diabetes mellitus or impaired glucose tolerance [29]. In a study including white subjects, Casellini and colleagues [30] measured ESC in 83 patients with type 1 or type 2 diabetes and 210 controls. In receiver operating characteristic (ROC) curve analysis, ESC measurements (feet ESC cutoff 77 µS) showed sensitivity of 78% and specificity of 92% for detecting diabetic neuropathy using the Neuropathy Impairment Score-Lower Limbs as a reference. Another study in 394 Chinese subjects with type 2 diabetes mellitus showed that ESC values decreased with increasing scores of the Neurological Symptom Score ($R = -124$, $p < 0.05$) and Neuropathy Disability Score ($R = -0.3$, $p < 0.01$) [31].

Selvarajah and colleagues [32] evaluated 45 participants with type 1 diabetes mellitus and 25 healthy controls. Assessments included evaluation for the presence of diabetic peripheral neuropathy [33] and cardiac autonomic neuropathy with cardiovascular autonomic testing. The authors found that ESC in the feet was lower in subjects with diabetic peripheral neuropathy (53.5 ± 25.1 µS) than in patients without peripheral neuropathy (77.0 ± 7.9 µS) or in healthy controls (77.1 ± 14.3 µS, $p < 0.001$). Similarly, subjects with cardiac autonomic neuropathy had lower ESC results (55.0 ± 28.2 µS) than patients with no cardiac autonomic neuropathy (72.1 ± 12.2 µS) or healthy controls (77.1 ± 12.2 µS, $p < 0.001$).

Sheshah and colleagues [34] studied 296 Saudi patients with type 2 diabetes mellitus using the Neuropathy Symptom/Neuropathy Disability score. For values of ESC < 70 µS, the sensitivity/specificity for diagnosis of diabetic neuropathy was 67.5/58.9%. ESC values increased with increasing amplitude and velocity of peroneal and sural nerves ($p < 0.005$ in all cases).

Yajnik and colleagues [35] assessed ESC and its correlation with measures of peripheral and cardiac neuropathy in 265 Indian patients with type 2 diabetes mellitus. Lower ESC at the feet was associated with both increasing symptoms of peripheral neuropathy and worse physical disability scores. Lower ESC at the feet was also significantly associated with lower vibration sense perception ($p < 0.01$). Patients with abnormal cardiovascular autonomic testing had lower ESC ($p < 0.05$). Another study [36] including 232 patients with diabetes found that lower ESC values predicted abnormal cardiac autonomic responses with 92% sensitivity and 49% specificity. Ang and colleagues [37] assessed ESC in a longitudinal study of 37 patients with type 2 diabetes mellitus and 40 age-matched healthy controls. At baseline, there were no differences in ESC between patients with type 1 diabetes and controls, whereas heart rate variability and Valsalva ratios were significantly lower in the diabetic patients. Twelve months later, the patients with type 1 diabetes had experienced a significant decline in ESC ($p = 0.0006$ at hands and $p = 0.023$ at feet). However, no associations were found between ESC and other measures.

Non-diabetic neuropathy

Smith and colleagues [38] evaluated ESC in patients with symptoms consistent with distal symmetric polyneuropathy (22 patients with diabetes, two patients with pre-diabetes, and 31 patients with idiopathic neuropathy) as well as 42 controls. Patients were also assessed using QSART, nerve conduction studies, and skin biopsies. ESC was reduced in patients, and there was no difference between diabetic and non-diabetic subjects. Lower ESC values were associated with higher frequency of neuropathy signs using the Utah Early Neuropathy Scale (UENS $R = 0.388$, $p < 0.004$) and with symptoms using the Michigan Neuropathy Screening Instrument (MNSI $R = -0.398$, $p < 0.005$). Higher ESC values were associated with higher intra-epidermal fiber density (IENFD) at the proximal leg ($R = 0.373$, $p < 0.012$) but not the distal leg ($R = 0.263$). ESC results were significantly associated with the results of QSART at the foot ($R = 0.348$, $p < 0.015$). ESC also correlated with sural amplitude ($R = 0.337$, $p < 0.019$) but not with peroneal motor amplitude ($p < 0.068$) or peroneal motor conduction velocity ($p < 0.081$). ESC demonstrated sensitivity of 77% and specificity of 67% in detecting distal symmetric neuropathy using UENS as a reference.

In a prospective blinded study, Novak [39] investigated the association between ESC at the feet and ENFD and SGNFD at the distal leg using skin biopsies. The author also studied the association between ESC and QSART as well as symptom scales (neuropathy, pain, and autonomic). Eighty-one consecutive patients with small fiber neuropathy were included. ESC adjusted for weight was reduced in subjects with abnormally low ENFD (ENFD normal/abnormal, ESC $= 1.17 \pm 0.27/0.87 \pm 0.34$ µS/kg, $p < 0.0008$) and abnormally low SGNFD (SGNFD normal/abnormal ESC $= 1.09 \pm 0.34/0.78 \pm 0.3$ µS/kg, $p < 0.0003$). ESC adjusted for weight correlated with ENFD ($\rho = 0.73$, $p = 0.0001$) and SGNFD ($\rho = 0.64$, $p = 0.0001$).

ESC did not correlate with symptom scales. Castro and colleagues [40] studied ESC in 133 subjects with the Val-30Met mutation in the transthyretin familial amyloid polyneuropathy (TTR-FAP) gene, divided into asymptomatic and symptomatic stage 1 (walking unaided), which were compared with 37 healthy controls. ESC at the feet showed 76% sensitivity and 85% specificity (feet ESC cutoff 66 µS) for detection of autonomic dysfunction, defined as a score of 1 or above on the Compound Autonomic Dysfunction Test [41], which is a questionnaire evaluating symptoms of dysautonomia.

Interventional studies

Two studies used ESC to monitor the effect of therapeutic interventions. The first [42] evaluated the effect of disease-modifying anti-rheumatic drugs on ESC in 42 patients with rheumatoid arthritis, 18 with ankylosing spondylitis, and 30 aged-matched controls. In addition to ESC measurements, the authors performed sympathetic (blood pressure response to standing and handgrip test) and parasympathetic function tests (heart rate response to paced deep breathing and to the Valsalva maneuver). After a 12-week open-label period of administration of disease-modifying anti-rheumatic medication, parasympathetic and ESC measurements in the patient groups increased. The second study [43] evaluated the impact of bariatric surgery on cardiac autonomic tone, ESC, and sensory function in obese subjects with and without type 2 diabetes mellitus. Patients were evaluated at baseline and 4, 12, and 24 weeks after vertical sleeve gastrectomy or Roux-en-Y gastric bypass. Subjects were assessed using ESC, time- and frequency-domain heart rate variability analysis, Neuropathy Impairment Score of the Lower Legs (NIS-LL), quantitative sensory testing, and sural nerve conduction studies. Seventy subjects completed up to 24 weeks of follow-up (24 without type 2 diabetes mellitus, 29 with pre-diabetes, and 17 with type 2 diabetes mellitus). ESC of the feet was significantly higher in type 2 diabetic subjects (baseline vs. 12-week vs. 24-week, $p < 0.005$). Heart rate variability also increased significantly only in patients with type 2 diabetes. Basal heart rate, weight, body mass index, percentage of body fat, waist circumference, and high-density lipoprotein improved in all groups. These two studies suggest that ESC measurements can detect changes after specific therapeutic interventions, opening the door to its use as a potential outcome measure in clinical trials of diabetic and non-diabetic patients with sudomotor dysfunction.

Discussion

This systematic review was undertaken to evaluate studies using ESC measurements and to provide an evidence base to inform the use of this technique for the evaluation of sudomotor dysfunction.

ESC reflects the flow of chloride ions provoked by electric current. A study that included patients with cystic fibrosis [20] showed that ESC values were increased compared to those of controls. Because the sweat chloride concentration in patients with cystic fibrosis is increased [39, 44, 45], this ESC result is consistent with the assumption that ESC reflects changes in the concentration of sweat chloride. Thus, ESC values appear to reflect sweat gland dysfunction, which can be caused by both neurological and non-neurological disorders. Chronic denervation also results in atrophy of the sweat glands. Sweat glands are prone to atrophy and hypertrophy as a result of several non-neurological disorders [46]. Therefore, reduced ESC measurements may be caused by several mechanisms, including loss of sudomotor fibers, sweat gland atrophy, reduced number of sweat glands, or glandular dysfunction caused by toxic, metabolic, or other disorders.

Only one study in this review was found to have level-1 quality. This study demonstrated that ESC measurement correlated with sweat gland nerve fiber density [39], but also with the density of epidermal small fibers [39] unrelated to sweat production. The latter correlation may be due to a common offending factor causing both reduced sweat gland and epidermal nerve density. This study thus strongly suggests that ESC measurements could be used to monitor the severity of small fiber neuropathy, provided that non-neurological disorders of the sweat glands have been ruled out. In any case, further confirmatory studies are needed.

The studies included in this review that used ESC in patients with diabetes were of level-3 and level-4 quality. Many of the studies reported associations between lower ESC measurements and higher severity of kidney disease [22, 23, 25] or metabolic syndrome [21, 28]. There are two potential explanations for this. The most apparent is that the sudomotor small nerve dysfunction measured by ESC and the presence of metabolic or end-target organ damage are all comorbid consequences of the same disorder (i.e., diabetes), and that all are expected to progress in parallel. Therefore, in patients with diabetes, worse renal function (or the presence of metabolic syndrome) might be associated with lower ESC values, because both are surrogate markers of disease progression in patients with diabetes. The other—perhaps less likely—explanation is that, in these patients, reduced ESC measurements reflect sweat gland dysfunction due to metabolic derangement rather than sudomotor small fiber dysfunction. In this case, ESC would be directly activating the sweat gland but not the sudomotor fibers innervating the sweat glands. At this time, the evidence is not sufficient to provide a conclusive answer to this question, as the studies measuring ESC,

kidney disease, and metabolic syndrome in patients with diabetes did not measure sudomotor function with an established test.

A theoretical model suggests that ESC does stimulate small fibers directly [9, 18, 47], and there is experimental evidence that electric current directly stimulates the small fibers, at least in part. In isolated monkey eccrine sweat glands with preserved innervation [48], atropine administration reduced sweat secretion induced by electric current in 70% of sweat glands, proving that sudomotor cholinergic innervation plays a dominant role in electrical stimulation. The remaining (30%) sweat glands continued to secrete at a lower rate (15% of maximum), which suggests the presence of non-cholinergic transmission (i.e., adrenergic) or non-neural effects of electrical stimulation. The latter observation would suggest that even if an electric field stimulates the sweat gland directly, the effect is likely a minor compared to the effect due to stimulation of the sudomotor cholinergic nerves.

On the other hand, the level of electrical stimulation required to stimulate sweat production in humans appears to be high enough to also activate nociceptive afferent fibers, i.e., electrical stimulation in humans does not produce sweat unless the stimulation is sufficient to cause pain [49]. The voltage and intensity of ESC measurements are too low to be detected by fine touch or nociceptive fibers. A potential explanation for this discordant observation is that the ESC apparatus uses a direct current of variable intensity, whereas the above-mentioned study in humans [49] used repetitive stimulation.

Therefore, whether ESC stimulates sudomotor fibers or sweat glands directly is not absolutely clear. Designing a study using anticholinergic medications to confirm that ESC stimulates sudomotor fibers (i.e., ESC will be reduced) and not sweat glands (ESC should be unchanged) should be relatively straightforward. This design was already used to demonstrate that electrical stimulation of the lacrimal gland in rabbits activated small fibers (both efferent and afferent) and not the lacrimal gland per se, since the stimulation effect was eliminated with cholinergic muscarinic blockers [50]. It would also be useful to assess ESC in patients with congenital absence of sweat glands [51] or congenital absence of cholinergic sudomotor nerves (e.g., congenital insensitivity to pain and anhidrosis) [52].

Even if ESC stimulates the sweat glands directly and not small fibers, or if it stimulates both, it still may be a useful test: sweat glands are an end-organ of small cholinergic fibers, and degeneration of small fibers can result in sweat gland atrophy [46], affecting ESC. Furthermore, it is important to establish how clinical improvement in patients with small fiber neuropathies and re-innervation of sweat glands affects ESC. In either scenario, prospective studies are required to improve our interpretation of ESC

measurements. Figure 2 summarizes the potential mechanisms of ESC.

Similarities to and differences from other available techniques

This systematic review shows that there was considerable heterogeneity in the use of reference tests for comparison with ESC, and in many studies established sudomotor tests were not used. Table 3 summarizes the features of well-established techniques for measuring sudomotor functions.

Comparison with QSART

Both QSART and ESC use sweat glands as a proxy for small fiber dysfunction. QSART measures the sweat volume and uses acetylcholine as a mediator, which stimulates postganglionic fibers via muscarinic receptors [53]. ESC measures chloride ion flow in the skin and uses the electric current as a stimulus. In addition to the different measurement techniques, a major difference between QSART and ESC is that QSART uses chemical while ESC uses electrical stimuli. ESC appears to generate an exact level of electrical stimulation via the feedback of electrical drivers. This is in contrast to the QSART, where the number of molecules of acetylcholine delivered and measured may vary from measurement to measurement, since the iontophoretic driver used for acetylcholine delivery does not use a chemical feedback control.
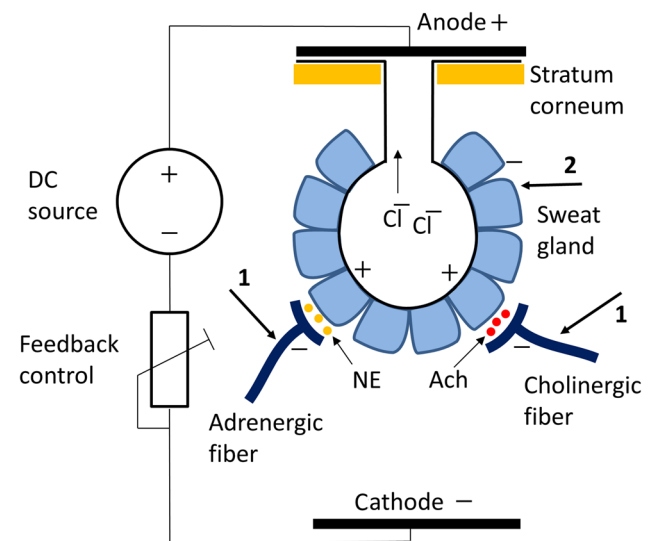
Fig. 2 Principles of ESC measurements. There are two proposed targets of stimulation. The sympathetic sudomotor fibers (cholinergic and adrenergic, with the majority cholinergic) are stimulated by electric current (1). The activated fibers stimulate sweat glands that release NaCl. Alternatively, the sweat glands are stimulated directly (2). Cl is then extracted by the anode, and the chloride ion flow is measured. *Ach* acetylcholine, *NE* norepinephrine

Table 3 Comparison of tests for the evaluation of small fiber function or density

Variable	QSART	SSR	TST	ESC	ENFD	SGNFD
What it measures	Sweat volume	Skin potential	Sweat distribution	Skin conductance	Epidermal small fiber density	Sweat gland small fiber density
Stimulus	Acetylcholine	Electric current	Temperature	Electric current	None	None
Complexity	High	Low	Very high	Very low	Low[a]	Low[a]
Nervous system region tested	Postganglionic	Central and peripheral	Pre- and postganglionic	Postganglionic	Peripheral	Postganglionic
Reproducibility	Limited	Poor		High	High	Not known
Correlation with ESC	Mildly or not	Unknown	Unknown	–	Yes	Yes
Quantitative and allows grading of abnormalities	Yes	No	Limited	Yes, but grading to be proven	Yes	Yes
Enables symmetry evaluations	Yes	Yes	Yes	Yes	Yes	Yes
Length-dependent pattern	Yes	No	Yes	No	Yes	Yes
Longitudinal studies using as outcome measure	No	No	No	Yes, limited	Yes	No
Sensitivity to medication	Yes	Yes	Yes	Probably yes	No	No

[a] The performance of the biopsy is relatively non-complex; the biopsy processing is complex but can be done externally

Another difference between QSART and ESC, although of unclear clinical significance, is the fact that QSART uses a pure cholinergic stimulus (acetylcholine), whereas the electrical stimulation used in ESC, in theory, could stimulate both cholinergic and adrenergic sudomotor fibers, even if the latter are a minority [13, 54]. Furthermore, ESC provides measurements at the palms and soles, which are under emotional control of sweating [55, 56], whereas QSART mainly assesses thermoregulatory sweating at the proximal and distal limbs [53]. Surprisingly, studies thus far have shown little or no correlation between ESC and QSART [39, 44]. The differences in measurement principles between tests as discussed above may play a role. Another unexplained difference between QSART and ESC is that QSART is much more sensitive to age and gender. Further studies may help provide greater clarity regarding the relationship between these two tests.

Comparison with SSR

Both SSR [57] and ESC rely on electrical recordings from the surface of the skin. The SSR response can be triggered by an inspiratory gasp, forceful expiration, or electrical stimulation. SSR is believed to be generated by a reflex activation of sweat glands via cholinergic sudomotor fibers. The SSR is a multi-synaptic reflex, and therefore depends on the integrity of both the peripheral and central nervous systems. Abnormal SSR could result from abnormal autonomic efferent fibers, abnormal sensory afferent fibers, or atrophy of effector sweat glands after chronic denervation [58]. SSR has a number of limitations: it is qualitative in nature, with poor reproducibility, is clearly inferior to QSART for the evaluation of sudomotor function [54–57, 59], and may be normal in patients with absent sweat glands [60]. As a screening tool for sudomotor dysfunction in the context of a small fiber neuropathy, ESC appears to be superior to SSR, as ESC is reproducible, fully quantitative, without habituation, requires minimal patient cooperation, and is more sensitive than SSR for the diagnosis of small fiber neuropathy (sensitivity/specificity 49.4/92.5% for ESC vs. 33.3/77.6% for SSR) [61].

Comparison with TST

TST measures the integrity of both the central and peripheral nervous systems [57]. A major disadvantage of TST is the requirement for a complex setup. However, TST is unique in that it provides sweating topography. ESC and TST have different objectives, and it is not expected that ESC will replace TST, as ESC measurements are restricted to hands and feet, and do not assess the integrity of the CNS.

Comparison with skin biopsies

A prospective blinded study showed a correlation between ESC and both SGNFD and ENFD [39]. Another study showed a correlation between higher ESC values at the feet and higher ENFD at the thigh, but not ENFD at the calf [44]. The direct functional–pathological correlation (ESC-SGNFD), although moderate ($R = 0.64$, $p = 0.0001$) [39], supports the notion that ESC reflects sudomotor fiber dysfunction. This correlation was obtained after adjusting the ESC by weight, indicating that weight or related metrics (BMI, size of the measured area, etc.) may be a confounder. Clinicians should exercise care when interpreting interventional studies if patient weight changes over time.

Potential advantages

Because of the high reproducibility of ESC, potential advantages include the capacity for grading of abnormalities and the use of ESC values as longitudinal measurements for assessing disease progression. Two interventional studies—one investigating bariatric surgery in patients with obesity [43] and the other examining disease-modifying anti-rheumatic drugs in patients with arthritis [62]—showed improvement in ESC abnormalities post-treatment. However, neither study performed established tests of sweat function to validate the ESC results. Also, future studies are needed to clarify whether ESC is able to detect sudomotor re-innervation.

Recommendations

Although a burgeoning body of evidence suggests that ESC can accurately measure sudomotor function, and that it correlates with SGNFD and ENFD, most studies thus far are of limited quality. In this review, only one study was blinded, and all but two failed to include consecutive patients or to use other well-established sudomotor function tests as reference. Furthermore, studies evaluating the effect of medication that can affect sudomotor function—particularly anticholinergic medication—are lacking. Thus future studies should (1) recruit consecutive patients, (2) perform the analysis and interpretation of data blinded to the suspected diagnosis, and (3) include established tests of sudomotor function and/or skin biopsy. Cardiovascular autonomic testing (heart rate variability during paced deep breathing, Valsalva maneuver, and tilt-table test) should be performed in patients with suspected cardiovascular autonomic failure [7]. ESC must never replace cardiovascular autonomic testing under any circumstances, as each technique measures different outcomes. Most of the ESC studies were funded by the device manufacturer, raising concerns about potential industry bias. Non-industry-sponsored studies would be ideal.

Conclusions

A growing body of evidence suggests that ESC measurements have the potential for use in evaluating sudomotor function. The European Network for TTR-FAP (ATTReuNET) recommends evaluation of asymptomatic carriers for the presence of small fiber damage using ESC measurements as an alternative to SSR or QSART [63]. Our review of this evidence can now be used to inform recommendations for sudomotor testing. Fully quantitative, noninvasive, and simple methods are needed for the detection of SFN and related autonomic dysfunction. A number of studies indicate the clinical potential of ESC. The association between ESC and SGNFD, along with the high reproducibility of ESC measurements, is particularly promising. At the same time, clinicians using ESC measurements must be aware of some caveats. ESC provides an index of sudomotor activity, and should in no way be considered a replacement for established gold-standard cardiovascular autonomic tests (heart rate variability during paced deep breathing, Valsalva maneuver, and tilt-table testing) for the assessment of cardiovascular autonomic function. Although the ESC correlates with skin biopsies assessing small fibers, the correlation is not high enough to justify replacement of skin biopsies by ESC. Moreover, ESC measurements may be abnormal in patients with abnormal sweat composition (e.g., cystic fibrosis) but otherwise normal sudomotor function. Although existing studies suggest that ESC is superior to SSR, important knowledge gaps remain, as the quality of the evidence regarding the relationship between ESC and QSART or SSR needs to be clarified.

Compliance with ethical standards

Conflict of interest The Sudoscan® device was donated to the author by Impeto Medical. Dr. Novak has received funding support from Impeto Medical.

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