

Electrochemical skin conductance by Sudoscan®: a new tool to predict intradialytic hypotension

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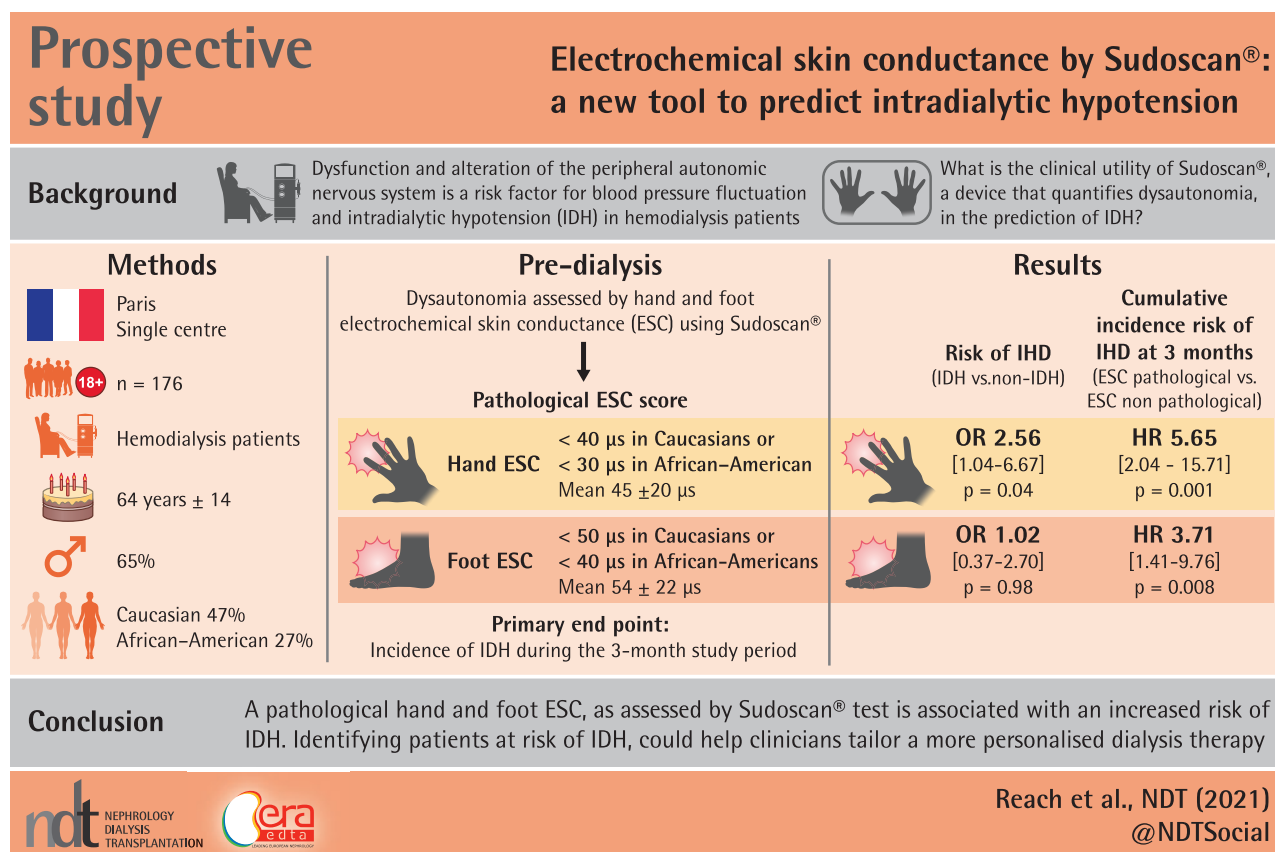
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GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What is already known about this subject?

- dysfunction and alterations of the peripheral autonomic nervous system are responsible for blood pressure fluctuations and intradialytic hypotension (IDH) in haemodialysis patients. Simple tools to detect and quantify the severity of dysautonomia are lacking.

What this study adds?

- we investigated the clinical utility of Sudocan[®], a device that quantifies dysautonomia. We showed that a pathological hand or foot electrochemical skin conductance assessed by the Sudocan[®] is associated with an increased risk of IDH.

What impact this may have on practice or policy?

- Sudocan[®] is a simple non-invasive device that can be used to assess dysautonomia in HD patients. The identification of patients at risk of IDH could help clinicians to tailor a more personalized dialysis therapy.

ABSTRACT

Background. Intradialytic hypotension (IDH), a common complication in haemodialysis (HD) patients, is associated with multiple risk factors including cardiac dysfunction and alterations of the peripheral autonomic nervous system. To what extent dysautonomia may contribute to the occurrence of IDH remains elusive. We sought to investigate the clinical utility of Sudocan[®], a device that quantifies dysautonomia, in the prediction of IDH.

Methods. We conducted a prospective monocentric study in adult HD patients from July 2019 to February 2020. Dysautonomia was assessed by the measurements of hand and foot electrochemical skin conductance (ESC) using Sudocan[®], before HD. The primary endpoint was the incidence of IDH (The National Kidney Foundation/Kidney-Dialysis Outcome Quality Initiative definition), according to the presence of a pathological hand and/or foot ESC value, during the 3-month study period.

Results. A total of 176 HD patients (64 ± 14 years old) were enrolled. Mean pre-dialysis HD hand and foot ESC was 45 ± 20 and 54 ± 22 μS, respectively. About 35% and 40% of patients had a pathological ESC at the hand and foot, respectively. IDH occurred in 46 patients. Logistic regression showed that pathological pre-dialysis HD hand ESC was associated with an increased risk of IDH [odds ratio = 2.56, 95% CI (1.04–6.67), P = 0.04]. The cumulative risk incidence of IHD during the study was 5.65 [95% CI (2.04–15.71), P = 0.001] and 3.71 [95% CI (1.41–9.76), P = 0.008], with a pathological hand and foot ESC, respectively.

Conclusions. A pathological hand ESC, as assessed by a non-invasive Sudocan[®] test, is associated with an increased risk of IDH.

Keywords: dialysis, electrochemical skin conductance, intradialytic hypotension, Sudocan[®]

INTRODUCTION

Intradialytic hypotension (IDH) is a common complication in haemodialysis (HD) patients. Depending on the definition of IDH, a recent meta-analysis estimated that the prevalence was <15% (10.1% based on the nadir₉₀ definition, or 11.7% based on with the European Best Practice guidelines) [1–3]. Its occurrence is associated with cardiovascular or neurological events, reduced dialysis dose, vascular access thrombosis and increased risk of mortality [4–6]. Various definitions of IDH have been used across studies. The National Kidney Foundation/Kidney-Dialysis Outcome Quality Initiative (NKF/K-DOQI) defined IDH as a decrease in arterial systolic blood pressure (SBP) >20 mmHg, compared with the initial value, and associated with clinical signs (muscle cramps, abdominal pain, loss of consciousness and convulsions) [7]. While this definition is widely accepted and used, another definition, the nadir of SBP of 90/100 mmHg, seems to be better correlated with mortality [5].

Several clinical features have been proposed to predict the risk of IDH, including age, comorbidities [diabetes and coronary artery disease (CAD)], type of dialysis [HD or haemodiafiltration (HDF)], dialysis parameter [dry weight, ultrafiltration rate (UFR) and sodium conductivity in the dialysate fluid] as well as alterations of the autonomic nervous system, especially the sympathetic system [1, 2, 8, 9]. Several mechanisms (e.g. alterations in central integration of the spinothalamic pathways, baroreceptor dysfunction) are responsible for BP fluctuations during dialysis [8]. These factors have already been studied in relation to HD and are directly correlated with the UFR [1, 8].

Over recent years, the study of vegetative functions has been facilitated by the use of Sudocan[®] (Impeto, Paris, France). It is a simple non-invasive device that allows the measurement of electrochemical skin conductance (ESC) by chloride ions, and

directly reflects the activity of small non-myelinated C nervous fibres that innervate the sweat glands [10]. Sudoscan[®] has been shown to have good sensitivity and specificity in the diagnosis of vegetative neuropathy in diabetic patients, and to be well correlated with autonomic cardiac neuropathy [10, 11]. This sensitivity is comparable to that of quantitative sensitive tests and the correlation with cardiovascular dysautonomia tests is also acceptable. There is a good correlation between Sudoscan[®] results and the reduction in the density of intra-dermal nervous fibres measured on skin biopsies [12, 13]. Additionally, this quick and easy test does not require the active participation of the patient.

HD patients are at risk of peripheral neuropathy not only because of an increasing incidence of diabetes (30–40%) but also because of the abnormal production and elimination of uraemic toxins [14]. Few studies have investigated the involvement of the vegetative nervous system on HD. A recent publication suggested a difference in nervous excitability depending on the type of HD (HD versus HDF) [15]. However, to what extent dysautonomia may contribute to the occurrence of IDH is not known. Identifying patients at risk of discomfort during HD sessions could be useful in adapting HD protocols. In this study, we evaluated the potential of Sudoscan[®] as a tool to identify HD patients at risk for IDH.

MATERIALS AND METHODS

Patients

We initiated a single-centre observational prospective study of adult HD patients (>18 years old), over a 6-month period (from July 2019 to February 2020). All consecutive adults in chronic HD in AURA Paris Plaisance centre were reviewed. Inclusion criteria were patients on HD >6 months. Exclusion criteria were (i) local complications (foot ulcer and amputation), (ii) inability to give oral consent and (iii) inability to stand during the test duration.

Data collection

We collected patients' epidemiological and laboratory data using our medical informatics record system (Hemodial, PHP development, France and Medial, Nantes, France).

Demographic data collected were: age, sex, ethnicity, initial nephropathy, diabetes, type of diabetes (T1D or T2D), diabetes duration, CAD, hypertension, pacemaker, body mass index (BMI), HD vintage, HD technique (HDF or HD), dialysis time, dry weight and interdialytic weight gain (IDWG), UFR, SBP and diastolic BP (DBP) pre/post-dialysis (measured by the nurse and recorded in our medical record) and the use of anti-hypertensive drugs [beta-blocker, renin-angiotensin-aldosterone system (RAAS) blocker and calcium channel blocker].

Measurements of ESC by sudoscan[®]

Sudoscan[®] assesses the electrochemical reaction between the chloride ions released by the sweat glands innervated by amyelinated C fibres and two large stainless-steel electrodes in contact with the hands and feet. This is a non-invasive test and requires 2 min during which four combinations of 15 different low-

voltage direct currents are applied. The subject places the palms of the hands and soles of the feet on the electrodes. The skin conductance is expressed in micro Siemens (μ S) and corresponds to the ratio of the currents generated and applied to the electrodes. Sudoscan[®] measures both ESC at the hands and feet.

ESC measurements of the hands and feet by Sudoscan[®] (IMPETO) were acquired before HD and within 30 min after the end of HD.

The Sudoscan[®] measurement also provides a cardiac autonomic neuropathy (CAN) score, which reflects the degree of sympathetic and baroreceptor dysfunction. This score predicts subclinical CAN with a sensitivity of 83% and specificity of 63% [11].

According to the manufacturer's data and publication, ESC values are not influenced by sex, BMI and body temperature. There is a slight increase (10%) of ESC values under stress conditions such as exercise [16, 17]. The main factors that influence the ESC value are ethnicity [10]. Therefore, we define a pathological ESC, by:

- a hand ESC value <40 μ S in Caucasians or <30 μ S in Afro-American and Caribbean subjects.
- a foot ESC value <50 μ S in Caucasian or <40 μ S in Afro-American and Caribbean subjects.

The distribution of ESC values is represented in [Supplementary data, Figure S1](#). To rule out any intra-individual variability, we measured ESC by Sudoscan[®] on two different days of the week for the first 30 patients. No difference was observed ([Supplementary data, Figure S2](#)). Subsequently, Sudoscan[®] was performed independently of the day of dialysis. The baseline Sudoscan[®] value was the exposure of interest.

IDH definition during follow-up

IDH was defined by a >20 mmHg drop in SBP with symptoms of dizziness, nausea, vomiting, blurred vision, cramps or syncope during the dialysis session, according to the NKF/K-DOQI definition [7]. We also collected IDH according to the SBP nadir 90/100 mmHg definition [5]. The nadir 90/100 mmHg is defined as a minimal intradialytic SBP at 90 mmHg if the initial SBP is >160 mmHg or a minimal intradialytic SBP at 100 mmHg if the initial SBP is >170 mmHg. The occurrence of IDH was assessed 3 months after the measurement of the baseline ESC.

Ethical statement

The study sponsor was the Groupe Hospitalier Paris Saint-Joseph. The study was approved by the institutional ethics committee (institutional review board number IRB00012157) and registered on the French health data hub. All patients were given information by their physicians. The patient's non-opposition to the use of their data for research was also collected in accordance with European regulations (General Data Protection Regulation).

Statistical analysis

Group statistics for continuous measures was reported as mean \pm standard deviation (SD) for normally distributed

measures or as median [interquartile range (IQR)] otherwise; categorical measures were reported as counts (percentage). Comparisons between patients were performed using a parametric test (Student's *t*-test), non-parametric test (Mann–Whitney test) or chi-square test, and Fisher's exact test when appropriate.

We fitted a logistic mixed model using the *glm* function from the statistics implemented in the R software package. Modelling for NKF/K-DOQI definition was adjusted for age, insulin, atrial fibrillation (AF), BMI (continuous variable), use of calcium channel blockers, history of IDH, SBP pre-dialysis HD foot and hand ESC, pre-dialysis HD cardiomyopathy score and diabetes. Modelling for nadir_{90/100} was adjusted for age, AF, BMI (continuous variable), use of calcium channel blockers, history of IDH, mean arterial pressure, UF, IDWG and diabetes.

Cumulative risk incidence curves were drawn and survival functions (survfit) were compared using a Cox model (*coxph* function). We tested the proportional hazard assumption by using the Schoenfeld residuals. When this assumption was not true, we stratified our models according to time.

All tests were two-sided and a *P*-value <0.05 was considered significant. Statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Over the 6-month period, 281 HD patients were screened. A total of 176 patients (62%) were included in the final analysis (see Flowchart [Supplementary data, Figure S3](#) and [Supplementary data, Table S1](#) for baseline characteristics of included and excluded patients). Baseline demographic and biological characteristics of the included patients are listed in [Table 1](#). The mean age was 64 ± 14 years old. There were 65% men and most were Caucasian (47%). Diabetes was observed in 69 patients (39%) with 38 (22%) of them receiving insulin therapy. CAD and AF were present in 56 (32%) and 33 (19%) patients, respectively. The median HD vintage was 51 months (range 20–101). Most patients (89%) were on HDF.

Mean pre-dialysis HD hand ESC was 45 ± 20 and 54 ± 22 μS in the foot. Mean CAN was 33 ± 13%. A pathological hand and foot ESC was observed in 62 (35%) and 70 (40%), patients, respectively. Patients with diabetes had a lower hand and foot ESC 39 ± 18 versus 48 ± 20 μS (*P* < 0.01) and 49 ± 21 versus 58 ± 21 μS (*P* < 0.01), respectively, when compared with non-diabetics ([Supplementary data, Figure S4](#)). The baseline characteristics according to the presence of a pathological ESC are resumed in [Supplementary data, Table S2](#).

IDH during follow-up

During the 3-month follow-up, 46 patients (26%) had at least one episode of IDH according to the NKF/K-DOQI definition. Baseline demographic and biological characteristics are listed in [Table 1](#). Patients with IDH tended to be older (69 ± 10 versus 63 ± 15 years old, *P* < 0.01), had a higher rate of AF (30% versus 15%, *P* = 0.02), took less calcium channel blockers (22% versus 38%, *P* = 0.02) and tended to receive more beta-

blockers (70% versus 56%, *P* = 0.11) when compared with patients without IDH. No difference in total dialysis UF was observed between either groups (2.5 ± 0.8 versus 2.2 ± 1 L, *P* = 0.1) as well as UFR (9.2 ± 3.3 versus 8.5 ± 3.9 L, *P* = 0.24).

Post-dialysis HD SBP and DBP were also lower in the IDH group than in the group of patients without IDH [128 ± 26 versus 144 ± 24 mmHg (*P* < 0.01) and 66 ± 14 versus 75 ± 16 mmHg (*P* = 0.001), respectively] ([Table 2](#)). Nadir intradialytic SBP and DBP were 86 ± 14 and 47 ± 11 mmHg, respectively. No change in pulse rate was observed between nadir intradialytic pulse (71 ± 13/min) and the pulse measured 30 min before the IDH (72 ± 12/min).

More patients in the IDH group had a pathological pre-dialysis HD hand ESC (53% versus 29%, *P* < 0.01). A similar trend was observed with the pre-dialysis HD foot ESC but this did not reach statistical significance.

However, the pre-dialysis HD CAN score was higher in IDH patients than in those without IDH (36 ± 13% versus 31 ± 13%, *P* = 0.03) ([Table 2](#)).

Pathological ESC and risk of IDH

To further investigate the association of ESC and the risk of IDH, we performed two different analyses. First, a logistic regression is presented in [Table 3](#). Because diabetes mellitus is a known risk factor, we added this variable despite it not being statistically significant in our univariate analysis. Age, diabetes, presence of AF, use of calcium channel blockers, IDH and pre-dialysis HD SBP or DBP were not associated with the risk of IDH. Only the presence of a pathological pre-dialysis HD hand ESC was associated with an increased risk of IDH [odds ratio (OR) = 2.56, 95% CI (1.04–6.67), *P* = 0.04].

Secondly, we estimated the 3-month cumulative incidence risk of IDH according to the presence or the absence of a pathological hand ESC ([Figure 1](#)). Since the proportional hazard assumptions were not validated for hand ESC and foot ESC, we stratified according to time, with a cut-off at 45 days, for the two models. After 45 days, HD patients with pathological hand ESC had a 5-fold increased risk of IDH [hazards ratio (HR) = 5.65, 95% CI (2.04–15.71)]. A similar result was also observed with the presence of a pathological foot ESC, with a 4-fold increased risk of IDH [HR = 3.71, 95% CI (1.41–9.76)] ([Figure 2](#)).

IDH according to the nadir (nadir_{90/100}) definition during follow-up

We also analysed the association of pathologic ESC findings and the risk of IDH according to the nadir_{90/100} definition. During the 3-month follow-up period, 35 patients had at least one episode of IDH according to this definition. Baseline demographic and biological characteristics of this subgroup are listed in [Supplementary data, Table S3](#).

Patients with IDH tended to be older (70 ± 10 versus 63 ± 15 years old, *P* < 0.01) and took fewer calcium channel blockers (17% versus 38%, *P* = 0.02) when compared with those without IDH. Total dialysis UF was statistically higher in patients with IDH (2.6 ± 1 versus 2.2 ± 1 L, *P* = 0.02).

Table 1. Patient characteristics and dialysis parameters

	Total (n = 176)	Non-IDH (n = 130)	IDH (n = 46)	P-value
Age (years)	64 ± 14	63 ± 15	69 ± 10	<0.01
Males, n (%)	115 (65)	87 (67)	28 (61)	0.46
Ethnic group, n (%)				
Caucasian	83 (47)	57 (44)	26 (57)	0.47
Asian	5 (3)	3 (2)	2 (4)	-
African American	48 (27)	39 (30)	9 (20)	-
Indian	5 (3)	4 (3)	1 (2)	-
Maghrebian	35 (20)	27 (21)	8 (17)	-
Nephropathy, n (%)				
Glomerulopathy	81 (46)	62 (48)	19 (41)	0.36
Diabetes	49 (28)	34 (26)	15 (32)	-
Amylosis	2 (1)	2 (2)	0 (0)	-
TIN	0 (0)	0 (0)	0 (0)	-
Vascular	39 (22)	27 (21)	12 (26)	-
Others				-
Diabetes, n (%)	69 (39)	47 (34)	22 (48)	0.16
T1D/T2D	4/65	3/47	1/22	0.16
Duration	16 (11–25)	16 (11–25)	21 (13–26)	0.68
Insulin, n (%)	38 (22)	24 (19)	14 (30)	0.09
Mean Hb1Ac	5.9 ± 1.3	5.9 ± 1.3	6.1 ± 1.3	0.24
CAD, n (%)	56 (32)	39 (30)	17 (37)	0.38
AF	33 (19)	19 (15)	14 (30)	0.02
Defibrillator	11 (6)	6 (5)	5 (11)	0.16
History of transplantation	21 (12)	18 (14)	3 (7)	0.19
BMI	26 ± 6	25 ± 6	27 ± 6	0.06
HIV, n (%)	11 (6)	10 (8)	1 (2)	0.29
HBV, n (%)	6 (3)	5 (4)	1 (2)	>0.99
HCV, n (%)	5 (3)	4 (3)	1 (2)	>0.99
Alcohol use, n (%)	17 (10)	12 (9)	5 (11)	0.77
Anti-hypertensive drugs, n (%)				
Beta-blockers	105 (60)	73 (56)	32 (70)	0.11
RAASi	78 (44)	58 (44)	20 (43)	0.89
Calcium channel blockers	60 (34)	50 (38)	10 (22)	0.04
Diuretics	77 (44)	57 (44)	20 (44)	0.89
Centrally acting	10 (6)	7 (5)	3 (7)	0.72
Type of epuration, n (%)				
Post-dilution HDF	123 (70)	92 (71)	31 (67)	0.92
Pre-dilution HDF	26 (15)	19 (15)	7 (15)	
Mixed dilution HDF	7 (4)	5 (4)	2 (4)	
HD	20 (11)	14 (11)	6 (13)	
Dialysis vintage	51 (20–101)	50 (17–102)	55 (30–87)	0.82
Dialysis parameters				
Time	220 ± 34	219 ± 34	220 ± 37	0.58
Sodium	138 ± 1	138 ± 1	138 ± 1	0.32
Calcium	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	0.53
Dialysate acid, n (%)				
Hydrochloric acid	159 (90)	115 (88)	44 (96)	0.25
Citric acid	17 (10)	15 (12)	2 (4)	
IDWG (kg)	1.8 (1–2.5)	1.8 (0.8–2.5)	2 (1.5–2.6)	0.17
UFR (mL/kg/h)	8.7 ± 3.3	8.5 ± 3.9	9.2 ± 3.3	0.24
History of IDH, n (%)				
High (>2 months)	1 (1)	0	1 (2)	0.53
Low (<2 months)	8 (5)	4 (3)	4 (8)	
Once	23 (13)	14 (11)	9 (20)	

Table 1 represents data of the total population (N = 176) and the subgroups according to the presence of an IDH (NKF/K-DOQI definition). HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; TIN, tubulointerstitial nephropathy; RAASi, RAAS inhibitor. All continuous values are expressed as mean ± SD except for HD vintage and IDWG, which are expressed as median and IQR.

Pre-SBP tended to be lower in the IDH group 138 ± 25 versus 147 ± 1 mmHg ($P = 0.07$). Post-dialysis HD SBP and DBP were also lower in this group [127 ± 27 versus 143 ± 24 mmHg ($P < 0.01$) and 66 ± 14 versus 74 ± 16 mmHg ($P < 0.001$), respectively] (Supplementary data, Table S4). Nadir intradialytic SBP and DBP were 82 ± 9 and 45 ± 12 mmHg, respectively.

The proportion of patients with a pathological hand and foot ESC tended to be higher in the IDH group but did not reach statistical significance (44% versus 33%, $P = 0.24$ and 46% versus 38%, $P = 0.42$, respectively) (Supplementary data, Table S4). The logistic regression analysis revealed that only a UFR >2250 mL/HD session was associated with the occurrence

Table 2. ESC values and clinical dialysis parameters according to the NKF/K-DOQI definition

	Total (n = 176)	Non-IDH (n = 130)	IDH (n = 46)	P-value
Pre-dialysis HD SBP (mmHg)	145 ± 22	147 ± 21	140 ± 25	0.08
Post-dialysis HD SBP (mmHg)	140 ± 26	144 ± 24	128 ± 26	<0.001
Pre-dialysis HD DBP (mmHg)	73 ± 15	75 ± 16	69 ± 14	0.03
Post-dialysis HD DBP (mmHg)	72 ± 16	75 ± 16	66 ± 14	0.001
MAP (mmHg)	97 ± 15	99 ± 14	91 ± 16	0.002
Pre-dialysis HD pulse (beat/min)	73 ± 13	74 ± 14	70 ± 10	0.09
Post-dialysis HD pulse (beat/min)	69 ± 12	68 ± 13	69 ± 11	0.53
Nadir intradialytic SBP (mmHg)	NA	NA	86 ± 14	NA
Nadir intradialytic DBP (mmHg)	NA	NA	47 ± 12	NA
Nadir intradialytic pulse (beat/min)	NA	NA	71 ± 13	NA
Pre-dialysis HD ESC hand				
Mean (µS)	45 ± 20	46 ± 19	39 ± 21	0.04
Pathologic	62 (35%)	38 (29%)	24 (53%)	<0.01
Pre-dialysis HD ESC foot				
Mean (µS)	54 ± 22	56 ± 21	49 ± 23	0.08
Pathologic	70 (40%)	45 (35%)	25 (54%)	0.02
Pre-dialysis HD cardiomyopathy risk				
Mean	33 ± 13	31 ± 13	36 ± 11	0.03
Pre-dialysis HD weight (kg)	76.4 ± 19	75.3 ± 18	79.5 ± 19	0.17
Post-dialysis HD weight (kg)	74.6 ± 18	73.6 ± 18	77.4 ± 19	0.22
Mean UF (L/h)	2.3 ± 1	2.2 ± 1	2.5 ± 0.8	0.10
Meal before dialysis (<2 h), n (%)	75 (43)	59 (45)	16 (35)	0.23

Table 2 represents data of the total population (N=176) and the subgroups according to the presence of an IDH (NKF/K-DOQI definition). All continuous values are expressed as mean ± SD. MAP, mean arterial pressure; NA, not applicable.

Table 3. Logistic regression (NKF/K-DOQI definition)

	OR (95% CI)	P-value
Age ≥65 years old	1.24 (0.51–3.01)	0.39
Insulin	1.85 (0.55–6.38)	0.32
AF	1.76 (0.68–4.44)	0.23
BMI	1.03 (0.93–1.13)	0.57
Calcium channel blockers	0.63 (0.24–1.58)	0.33
IDH history	1.71 (0.63–4.58)	0.28
Pre-dialysis HD MAP >98 mmHg	0.41 (0.17–0.96)	0.04
Pre-dialysis HD pulse ≥71 beats/min	0.84 (0.37–1.94)	0.68
Pathological pre-dialysis HD ESC hand	2.56 (1.04–6.67)	0.04
Pathological pre-dialysis HD ESC foot	1.02 (0.37–2.70)	0.98
Diabetes	0.64 (0.21–1.78)	0.40

A logistic regression was performed with dialysis-related variables between IDH and non-IDH (NKF/K-DOQI definition). MAP, mean arterial pressure.

of IDH [OR 5.66, 95% CI (1.82–19.52), P = 0.004]. It should be noted that the use of calcium channel blockers seemed to be protective [OR 0.30, 95% CI (0.10–0.83), P = 0.03] (Supplementary data, Table S5).

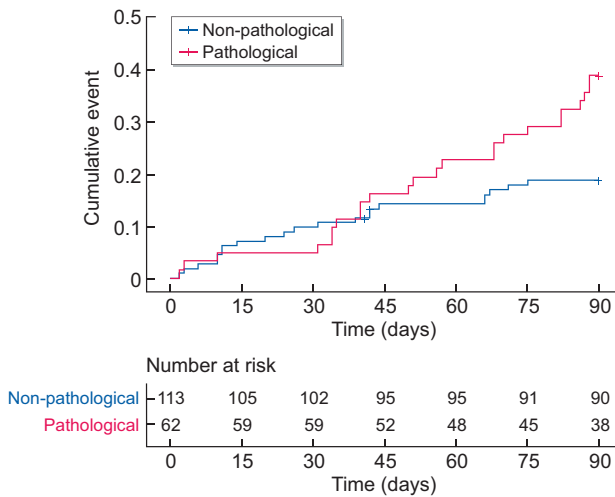
As the proportional hazard assumptions were not validated for the two models either, we stratified according to time, with a cut-off at 45 days. A significant difference was also observed after 45 days, with a 5-fold increased risk of IDH for HD patients with pathological hand ESC [HR = 4.56, 95% CI (1.40–14.82)] (Supplementary data, Figure S5) and a 4-fold increased risk of IDH for those with pathological foot ESC [HR = 3.86, 95% CI (1.19–12.55)] (Supplementary data, Figure S6).

DISCUSSION

The occurrence of IDH is associated with poor outcomes in HD patients and its prevention is a key consideration for clinicians

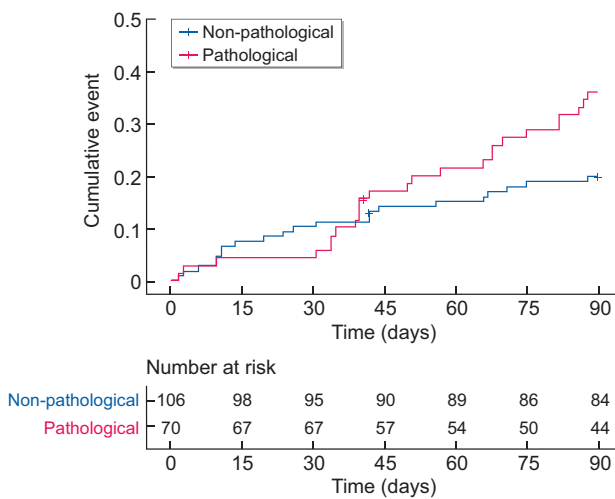
caring for these patients. Alterations of the autonomic nervous system have been recognized as an important predisposing factor for IDH. However, the availability of a simple reliable tool to assess the contribution of dysautonomia in the pathogenesis of IDH is lacking. In this study, we were able, for the first time, to objectively identify and quantify the presence of dysautonomia and to predict the risk of IDH in a HD population. Both pathologic hand and foot ESC were associated with a 2-fold increased risk of IDH (NKF/K-DOQI).

Evaluation of the autonomic nervous system can be conducted by several tests such as Valsalva manoeuvre, sympathetic skin response, thermoregulatory sweat and quantitative sudomotor axon reflex tests or heart variability. All of these tests are time-consuming and difficult to apply in clinical practice due to a low reproducibility [18]. The Sudoscan[®] procedure is an easy-to-perform evaluation, initially developed for diabetic populations in order to study early-stage peripheral polyneuropathy, small nervous fibre pathology and autonomic neuropathy [19]. It has also been tested and validated in non-diabetic populations with small nervous fibre pathology, such as patients with familial amyloid and Fabry disease [20]. A Chinese study of 2833 diabetic patients showed that the Sudoscan[®] device could be used on patients with chronic kidney disease (CKD) in order to detect incipient uraemic neuropathy and its long-term evolution towards CKD [21]. We also confirmed in our cohort that mean hand and foot ESC values were significantly lower in diabetic versus non-diabetic patients. In contrast to this, Vinik *et al.* [16] reported that ESC values were also abnormal in non-diabetic patients, suggesting the presence of an autonomic dysfunction secondary to other comorbidities. The measure of ESC was reproducible independent of either the day of dialysis or the time of HD (before versus after). Thus, only one single



	HR [CI 95%]	P
ESC hand pathological vs. ESC hand non-pathological before 45 days	1.13 [0.51; 2.50]	0.76
ESC hand pathological vs. ESC hand non-pathological after 45 days	5.65 [2.04; 15.71]	0.001

FIGURE 1: Cumulative incidence risk of IDH according to pathological hand ESC. The graph represents the cumulative incidence risk for IDH (NKF/K-DOQI) during the first 90 days of the study according to the presence (pink) or not (blue) of a pathological hand ESC.



	HR [CI 95%]	P
ESC foot pathological vs. ESC foot non-pathological before 45 days	1.20 [0.56; 2.57]	0.63
ESC foot pathological vs. ESC foot non-pathological after 45 days	3.71 [1.41; 9.76]	0.008

FIGURE 2: Cumulative incidence risk of IDH according to pathological foot ESC. The graph represents the cumulative incidence risk for IDH (NKF/K-DOQI) during the first 90 days of the study according to the presence (pink) or not (blue) of a pathological foot ESC.

measure of Sudoscan[®] seems necessary to quantify and assess the autonomic dysfunction.

Underlying cardiac conditions may also play a critical role in the occurrence of IDH. In our cohort, we observed more patients with AF in the IDH group than in the group of patients

without IDH. This is in agreement with the recent findings of Chang *et al.* [22] in the elderly general population. In our study, this difference did not reach statistical significance, probably due to the small study population size. Antihypertensive medications could theoretically mitigate or exacerbate IDH. However, it is not clear to what extent each drug increases the risk of IDH [23]. Surprisingly, we found that prescription of calcium channel blockers was associated with a lower risk of presenting IDH in the univariate analysis. This finding is in line with a previous study evaluating the use of amlodipine in HD patients [24]. Treatment such as beta-blockers may interfere and alter the sympathetic response during IDH, especially in diabetic patients. Indeed, we observed an association between the use of beta-blockers and the survey of IDH.

We might anticipate that dysautonomia would act in synergy with hypovolaemia and lead to a more severe drop in BP. Based on this hypothesis, a pathological ESC value would be associated with IDH regardless of the type of definition. However, our result did not support this hypothesis. The strong association of a pathological ESC and IDH occurrence was not observed with the nadir_{90/100} definition. Most definitions of IDH use at least one of the following components [1]: occurrence of low SBP below a certain threshold/nadir [2], intradialytic SBP decline [3], patient-reported intradialytic symptoms and [4] medical intervention during dialysis aimed at restoring blood volume (BV) [5]. The nadir_{90/100} score better predicted the risk of mortality than the NKF/K-DOQI and such a definition could be preferred for the kind of study performed here.

However, we strongly believe that the results obtained from these two definitions might highlight different mechanisms of IDH. Indeed, in the NKF/K-DOQI definition, the minimal drop of SBP must be >20 mmHg and associated with clinical symptoms. The drop of SBP may result from different mechanisms, including a 'classical' change in the BV related to UF or a low cardiac output related to either cardiac dysfunction or dysautonomia. However, in the nadir_{90/100} definition, the drop in BP is often higher than in the NKF/K-DOQI definition, as observed in our cohort. Thus, the change of SBP may mostly reflect a BV decrease secondary to an aggressive UF or insufficient refilling rate. This hypothesis may explain why we observed only an association of pathological ESC and IDH when using the NKF/K-DOQI definition of IDH.

Our study has several limitations. First, it is prospective single-centre study without external validation. Secondly, the use of Sudoscan[®] in HD patients has not been previously validated. Thirdly, several factors may have weakened our model. Diabetic patients with foot ulcers or amputations may have severe dysautonomia and were excluded from the study. Similarly, patients who were not able to stand were excluded from the analysis. Sarcopaenia or limited autonomy was the main cause of this inability. However, some of these patients may also have multiple comorbidities such as cardiovascular disease, or neurological disorders that are risk factors for IDH. Interestingly, because hand ESC seems to better discriminate patients at risk of IDH, it could be interesting to use hand ESC measurements only in these patients. Estimation of the intravascular volume decline either by bioimpedancemetry device or by BV monitoring was not available for all patients. Thus, we

could not assess to what extent hypovolaemia and dysautonomia contribute to the pathophysiology of IDH. Our current practice to prevent IDH also includes the adjustment of the dry weight according to the Δ Protidaemia, which is assessed monthly and could reduce the frequency of IDH in our population during the follow-up [25]. The association between pre-dialysis HD ESC and IDH was only significant after 45 days. This finding may be explained by the low number of events before this time point. Furthermore, as some physicians were aware of the ESC result, we could not exclude that it changes their fluid volume management strategy in patients with dysautonomia. Finally, most of our patients were on HDF, a dialysis modality that has been shown to reduce the risk of hypotension compared with conventional HD. HDF is known to improve haemodynamic status by its effect on blood temperature. Because all dialysis machines used in this study were calibrated to have a blood temperature at 36°C, we could not assess a potential effect of blood temperature on ESC values.

Notwithstanding, our study has several strengths, including the number of patients studied ($N=170$), the reproducibility of the measure using the SudoScan[®] device and the evaluation of our results through two different statistical models.

CONCLUSION

We report that abnormal hand and foot ESC measured by SudoScan[®] in HD patients increased the risk of IDH. This simple, non-invasive device can be used as a tool to assess dysautonomia in this population. Whether the identification of patients at risk of IDH with the SudoScan[®] device could help clinicians tailor a more personalized dialysis therapy requires further study.

SUPPLEMENTARY DATA

Supplementary data are available at [ndt](http://ndt.oxfordjournals.org/) online.

CONFLICT OF INTEREST STATEMENT

The authors declare no competing financial interest.

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Received: 9.1.2021; Editorial decision: 19.4.2021