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Association of Electrochemical Skin Conductance by Sudoscan and Cardiovascular Outcomes in Hemodialysis Patients

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INTRODUCTION

Autonomic dysfunction, especially cardiac autonomic neuropathy (CAN) is a common complication in patients with end stage renal disease, and a well-known risk factor for sudden death.[1] Diabetes mellitus is known to be the main cause, but other factors such as obesity, cardiovascular disease, uremia has been linked to CAN pathogenesis.[2]

CAN is a microvascular condition that results from lesions of the sympathetic and parasympathetic nerve fibers which innervate the heart and blood vessels. At the early stage, CAN is a subclinical disease demonstrated by a reduction in heart rate variability (HRV). The parasympathetic activity decreases leading to sympathetic nervous system predominance and resting tachycardia. In advanced stage, CAN is characterized by orthostatic hypotension, exercise intolerance, and silent myocardial ischemia that contributes to morbidity and mortality.[3]

A battery of cardiovascular autonomic reflex tests (HRV, Valsalva maneuver, and postural blood pressure testing) are recommended for longitudinal testing of the CAN.[4] However, all these tests are time-consuming and not easily performed at bedside in routine, even the HRV.

In chronic kidney disease, patients, including hemodialysis (HD) patients, CAN has been associated with all-cause mortally rate but its relationship with major adverse cardiovascular event (MACE) is still controversial.[5-8]

We recently reported for the first time, the clinical pertinence of the Sudoscan (Impeto, Paris, France) to assess dysautonomia to predict intradialytic hypotension.[9] Briefly, Sudoscan is a simple noninvasive device that allows the measurement of electrochemical skin conductance (ESC) by chloride ions, and directly reflects the activity of small nonmyelinated C nervous fibers which innervate the sweat glands. In a 24-month follow-up of the original cohort, we have now assessed the potential of Sudoscan to predict cardiovascular events and overall mortality in a single cohort of HD patients.

RESULTS

A total of 176 patients were included in the analysis. During the 24-month study, a first MACE occurred in 41 patients that included 3 strokes, 4 acute myocardial infarctions, and 37 deaths. The baseline demographic and biological characteristics according to the presence of patients with MACE are compared to those of patients without MACE (Supplementary Table S1). Briefly, patients with MACE were older (73±12 vs. 62±14 years old, $P < 0.001$), with more diabetes mellitus (56 vs. 34%, $P < 0.01$), and had a higher rate of

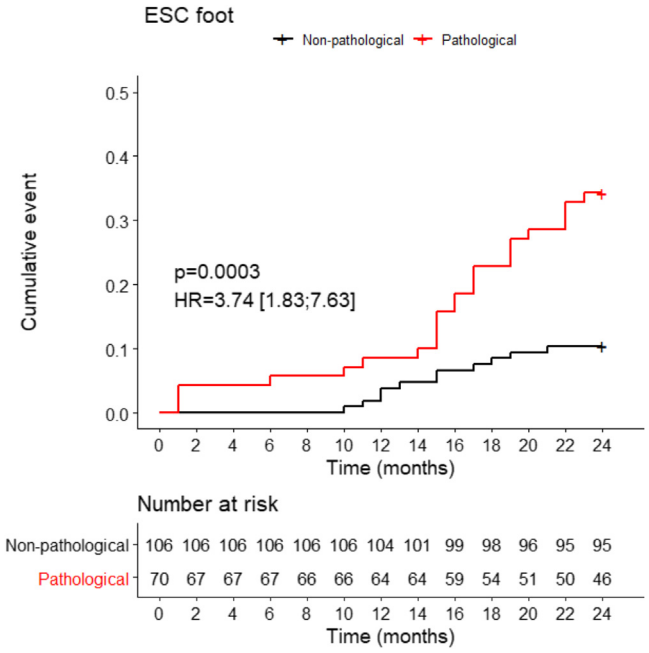

Figure 1. Cumulative incidence risk of death according to the presence of a pathological Foot ESC. The graph represents the cumulative incidence risk for death during the 24-month follow-up, according to the presence (red) or not (black) of a pathological foot ESC. HR, hazard ratio.

atrial fibrillation (34% vs. 14%, $P < 0.01$). Mean predialysis foot ESC was significantly lower in patients with MACE, than those with no MACE (47±21 mS vs. 57±22 mS, $P < 0.01$). No difference in the mean predialysis hand ESC (43±19 vs. 45±20 mS, $P = 0.34$) were observed between these 2 groups.

During the follow-up, 37 deaths were observed, including 10 from cardiovascular causes but none related to COVID-19. HD patients with pathological foot ESC had a 3-fold increased risk of death (hazard ratio [HR] = 3.74, 95% confidence interval [CI] 1.83–7.63, $P < 0.001$) (Figure 1). This association was confirmed with a multivariate Cox regression model which is presented in Table 1**.** A pathological pre-HD foot ESC was also associated with an increased risk of death (HR = 2.92, 95% CI 1.36–6.26, $P < 0.01$). Similarly, HD patients with pathological foot ESC had a 3-fold increased risk of MACE (HR = 2.88, 95% CI 1.49–5.56, $P < 0.01$) (Supplementary Figure S1 and Supplementary Table S2).

In contrast, no association was observed between a pathological pre-HD hand ESC and MACE (HR = 1.43, 95% CI 0.72–2.83, $P = 0.30$); or death (HR = 1.64, 95% CI [0.82–3.30], $P = 0.16$) (Supplementary Tables S3 and S4).

DISCUSSION

Our results are consistent with previous reports that underline the strong relationship between dysautonomia assessed by a decrease HRV (e.g., low frequency) and overall mortality. In both nondialysis and dialysis chronic kidney disease, studies have showed that some HRV measures were independent predictors of cardiac death.[5,S1] HRV is a noninvasive measure that is best assessed by continuous electrocardiography over a 24-hour period, although shorter recordings have also been utilized. The Sudoscan device has several advantages as compared to the other classical tests to evaluate CAN. The procedure is an easy-to-perform evaluation and reliable method. It can be performed either before or after the dialysis session in less than 2 minutes.[9]

Furthermore, although Sudoscan was not validated specifically in patients with atrial fibrillation, it could be a new tool to examine the autonomous nervous system in this population

We find a strong relationship between MACE and foot ESC, but not hand ESC. Diabetic neuropathy is typically a distal symmetric cause by a length-dependent axonopathy. Thus, the foot ESC may be more representative of the severity of the diabetic induced dysautonomia as compared to the hand ESC. Moreover, the presence of the arterio-venous fistula and/or a carpal tunnel syndrome may modify the hand ESC values. This is the subject of an ongoing study.

Our study has several limitations that has been already described previously.[9] Finally, our results are based on a prevalent cohort and should be validated ultimately in an incident cohort of HD.

In conclusion, besides its capacity to predict intradialytic hypotension, the Sudoscan appears as a promising, simple, noninvasive, and quick test that can be used in routine to predict mortality and cardiac events in HD patients.

Table 1. Death independent risk factors according to several predictors and predialysis foot ESC

Variables	HR [CI 95%]	*P*-value
Age ≥65.5 years old	2.32 [0.99; 5.41]	0.05
Diabetes mellitus	1.58 [0.80; 3.12]	0.19
Atrial fibrillation	1.82 [0.82; 4.04]	0.14
Alcohol use	1.62 [0.67; 3.93]	0.29
Dialysis time (≥ 240.00 vs. <240.00)	1.01 [0.50; 2.08]	0.97
Ultrafiltration (>800 ml/h)	0.60 [0.29; 1.26]	0.18
Pre dialysis MAP > 98 mm Hg	0.61 [0.29; 1.29]	0.20
IDH	1.12 [0.52; 2.42]	0.76
Pathological predialysis ESC foot	2.95 [1.41; 6.20]	<0.01

CI, confidence interval; ESC, electrochemical skin conductance; HR, hazard ratio; IDH, intradialytic hypotension; MAP, mean arterial pressure.
A multivariate Cox regression model was performed with dialysis-related variables and redialysis foot ESC to assess independent risk factors of death.
IDH defined by an history of IDH 3 months prior and after the inclusion and 3 months.; MAP mean arterial pressure; ESC: Electrochemical Skin Conductance.

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

The authors declare that they have obtained consent from the patients discussed in the report.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Cumulative incidence risk of MACE according to the presence of a pathological foot ESC.

Table S1. Patient characteristics and dialysis parameters.

Table S2. MACE independent risk factors according to several predictors and foot ESC.

Table S3. MACE independent risk factors according to several predictors and hand ESC.

Table S4. Death independent risk factors according to several predictors and hand ESC.

REFERENCES

1. Savica V, Musolino R, Di LR, et al. Autonomic dysfunction in uremia. *Am J Kidney Dis*. 2001;38(Suppl 1):S118–S121. https://doi.org/10.1053/ajkd.2001.27418
2. Robinson TG, Carr SJ. Cardiovascular autonomic dysfunction in uremia. *Kidney Int*. 2002;62:1921–1932. https://doi.org/10.1046/j.1523-1755.2002.00659.x
3. Chen HS, Hwu CM, Kuo BI, et al. Abnormal cardiovascular reflex tests are predictors of mortality in type 2 diabetes mellitus. *Diabet Med*. 2001;18:268–273. https://doi.org/10.1046/j.1464-5491.2001.00442.x
4. Proceedings of a consensus development conference on standardized measures in diabetic neuropathy. Summary and recommendations. *Diabetes Care*. 1992;15:1104–1107. https://doi.org/10.2337/diacare.15.8.1104
5. Chandra P, Sands RL, Gillespie BW, et al. Predictors of heart rate variability and its prognostic significance in chronic kidney disease. *Nephrol Dial Transplant*. 2012;27:700–709. https://doi.org/10.1093/ndt/gfr340
6. Suzuki M, Hiroshi T, Aoyama T, et al. Nonlinear measures of heart rate variability and mortality risk in hemodialysis patients. *Clin J Am Soc Nephrol*. 2012;7:1454–1460. https://doi.org/10.2215/CJN.09430911
7. Drawz PE, Babineau DC, Brecklin C, et al. E-mail heart rate variability is a predictor of mortality in chronic kidney disease: a report from the CRIC study. *Am J Nephrol*. 2013;38:517–528. https://doi.org/10.1159/000357200
8. Chang YM, Huang YT, Chen IL, et al. Heart rate variability as an independent predictor for 8-year mortality among chronic hemodialysis patients. *Sci Rep*. 2020;10:881. https://doi.org/10.1038/s41598-020-57792-3
9. Reach P, Touzot M, Lombardi Y, et al. Electrochemical skin conductance by Sudoscan®: a new tool to predict intradialytic hypotension. *Nephrol Dial Transplant*. 2021;36:1511–1518. https://doi.org/10.1093/ndt/gfab183