

Characteristics of cardiovascular autonomic dysfunction and association with quality of life in patients with systemic lupus erythematosus

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ABSTRACT

Objectives Cardiovascular autonomic neuropathy (CAN) may affect the clinical course of SLE leading to reduced quality of life. CAN is assessed by heart rate variability (HRV) measures and cardiovascular autonomic reflex tests (CARTs). In patients with SLE, we aimed to determine the characteristics of CAN and if CAN associates with health-related quality of life (HRQoL).

Methods Patients with SLE and healthy controls (HCs) were CAN tested with 5 min HRV and three CARTs to determine parameters reflecting parasympathetic and mixed sympathetic–parasympathetic function. Subjects were classified as having no, early or definitive CAN by having none, one or more than one abnormal CART, respectively. HRQoL as determined by the Short Form 12 (SF-12) was assessed in SLE.

Results Of 111 patients with SLE, 92 answered the SF-12 and 54 were matched with 54 HCs for characterisation of CAN. Definitive CAN was present in 24.1% (95% CI 15% to 37%) patients with SLE and 1.9% (95% CI 0.3% to 9.8%) HCs (OR 16.8, 95% CI 2.1 to 133.8, $p=0.008$). The corresponding prevalences of any CAN were 53.7% (95% CI 41% to 66%) and 22.6% (95% CI 13% to 35%). SLE patients with definitive CAN showed signs of mixed sympathetic–parasympathetic dysfunction, whereas patients without CAN primarily presented with impaired parasympathetic activity. Signs of parasympathetic as well as sympathetic–parasympathetic dysfunction were associated with low physical SF-12 component score (all: $\beta>0.211$, $p<0.05$). The mental SF-12 component score was not associated with any CAN indices.

Conclusions CAN was a frequent finding in SLE and associated to self-report on impaired physical HRQoL. Even patients without CAN showed signs of impaired parasympathetic function compared with controls.

INTRODUCTION

Dysfunction of the autonomic nervous system (ANS) is increasingly studied in rheumatic diseases, including SLE.^{1,2} Dysfunction of the ANS may present as impaired cardiovascular regulation, denoted as cardiovascular autonomic neuropathy (CAN).³ CAN is determined

Key messages

What is already known about this subject?

- Patients with SLE may experience low health-related quality of life and have to a varying degree dysfunction of the autonomic nervous system.
- In other disease groups, dysfunction of the autonomic nervous system is associated to low self-reported quality of life, which has not been studied in SLE.

What does this study add?

- More than half of patients with SLE presented with signs of autonomic dysfunction characterised by mainly parasympathetic impairment and in more severe cases also by sympathetic impairment.
- Autonomic dysfunction was associated to low self-reported quality of life regarding physical aspects.

How might this impact on clinical practice or future developments?

- This study supports emerging evidence of autonomic dysfunction as a distinct disease mechanism in SLE that may offer new therapeutic possibilities.

by golden standard cardiovascular autonomic reflex tests (CARTs)^{4,5} supplemented by calculation of heart rate variability (HRV) from 5 min resting electrocardiography recordings.³ In small-sized SLE populations, the prevalence of CAN ranged widely from 10% to 90%.^{1,2} The clinical correlates of CAN in SLE have not been fully established; however, in some studies, CAN has been reported to associate with disease activity, inflammation,^{6,7} autoantibodies,^{7,8} neuropsychiatric comorbidities and hypertension.⁹ Interestingly, reduction of pain and fatigue in patients with SLE by stimulation of the parasympathetic vagus nerve¹⁰ supports the notion that the ANS has potential to modulate clinical symptoms in SLE.

The European League Against Rheumatism recommends to include patient reported outcome measures on health-related quality

of life (HRQoL) in clinical studies on SLE.¹¹ Reports of low HRQoL in SLE may to some extent be attributed to CAN, as reduced HRV is correlated to low HRQoL in healthy subjects¹² as well as chronically ill patients.^{13–15}

We hypothesise that CAN is a prevalent finding in patients with SLE and is characterised by distinct abnormal measures of ANS dysfunction that associate with low HRQoL. We aim to describe the prevalence of CAN in SLE, to identify specific characteristics of CAN by comparison with healthy controls and to explore associations between such characteristics and HRQoL.

METHODS

Study population and design

This cross-sectional controlled study recruited patients with SLE from a prospective study of cardiovascular disease in SLE inpatients and outpatients, PLUSheart (Prospective Lupus Study on Cardiovascular Risk Factors), established in 2012–2013 at Copenhagen University Hospital, Denmark.¹⁶ Inclusion criteria were the revised 1997 American College of Rheumatology SLE classification criteria^{17,18} and age above 18 years. Pregnancy excluded participation. Of the 147 cohort patients, 4 had died and 32 refrained participation, leaving 111 for enrolment from October 2018 to March 2019.

For comparison, data from 100 control subjects were available for matching. The controls were recruited by public advertisements from Aarhus University Hospital, Denmark, originally serving as controls for a recent type II diabetes mellitus study, IMPACT (Immune Profile and Complication Risk in Type 2 Diabetes).¹⁹ IMPACT exclusion criteria were: infections (acute/chronic), end-stage renal failure, pregnancy, lactation and cancer (prior/current). For optimal patient-control comparison in this study, only SLE patients without cardiac arrhythmias fulfilling the IMPACT criteria and similar controls were matched by age and sex, leaving 55 subjects in each group.

Measures of ANS function

Assessments of ANS function were completed using the handheld Vagus device (Medicus Engineering, Aarhus, Denmark).²⁰ Through handheld electrodes, the device continuously recorded lead I electrocardiography (ECG) measurements with a sampling frequency of 1000 Hz. Assessing autonomic function were obtained through HRV and CARTs were based on calculating beat-to-beat intervals between R-peaks (RR intervals) from electrocardiographic traces during passive resting and active tests. All subjects abstained from smoking, alcohol and caffeine beverages on the day of test and larger meals 2 hours prior to testing.

Passive HRV tests

To perform the 5 min passive HRV test, all subjects relaxed for 5 min in supine position. HRV indices were determined by the pattern of changes in RR intervals between normal heart beats (NN intervals) analysed by time domain, using standard statistical descriptions, and

frequency domain, estimating the frequency-specific fluctuations in HRV.¹ Time domain analysis included: (A) the SD of NN intervals (SDNN) and (B) the square root of the mean of the squares of differences between adjacent NN intervals (RMSSD). Power spectral analysis based on autoregressive modelling included: (A) low frequency (LF) power (in the 0.04–0.15 Hz band), (B) high frequency (HF) power (in the 0.15–0.4 Hz band), (C) total power (TP) (≤ 0.4 Hz) and (D) the LF/HF ratio.

Parasympathetic nervous system (PNS) activity is reflected by RMSSD and HF.⁵ The SDNN, LF and TP are influenced by both PNS, sympathetic nervous system (SNS) activity and baroreceptor sensitivity.^{5,21} Although remaining controversial,⁵ LF/HF ratio is often considered to reflect the sympatho-vagal balance, with higher values reflecting sympathetic predominance and vice versa.²²

Active HRV tests

Following the passive HRV test, three CARTs were performed in the following order: (A) response to standing (RS) ratio: the ratio of the longest RR interval around 30 s of standing and the shortest RR interval around 15 s of standing, (B) expiration inspiration (EI) ratio: the ratio of the longest RR interval during expiration and the shortest RR interval during inspiration at a respiratory frequency of six breaths/min and (C) Valsalva manoeuvre (VM) ratio: the ratio of the longest RR interval after the VM and the shortest RR interval during the 15 s VM.²³ EI ratio reflects PNS activity, whereas the RS and VM ratios reflect both SNS and PNS activity.^{24,25}

To categorise pathological CART results, age-dependent cut-off values²⁶ were applied. CAN scoring was performed in subjects completing >2 CARTs. As recommended, two or more abnormal CARTs were classified as definitive CAN and one pathological CART as early CAN.⁴

Clinical examination

All subjects were interviewed on smoking status and current medication to identify substances possibly altering autonomic regulation.²⁶ Additionally, height, weight, hip and waist circumference, as well as blood pressure and heart rate were measured after 5 min supine (SLE) or sitting (controls) rest.

Patients with SLE were clinically evaluated to assess disease activity and accumulated organ damage using the 2K-edition of the SLE Disease Activity Index²⁷ and the (Systemic Lupus Erythematosus International Collaborating Clinics Group) SLICC Damage Index (SDI),²⁸ respectively.

Health-related quality of life

Patients with SLE reported on their perceived HRQoL by means of the self-administered 12-item Short Form (SF-12)²⁹ derived from the original SF-36.³⁰ The SF-12 allows calculation of a physical component score and a mental component score that both range from 0 to 100 (lowest to highest self-reported health) by adding

weighted scorings of the 12 individual items to a component specific constant.^{30 31}

Statistics

Continuous descriptive data are presented as mean and SD if normally distributed, and skewed data as median and IQR. HRV indices and CARTs were log-transformed to employ normal distribution for parametric analyses. Two-group comparisons of continuous variables were done by Student's t-test or Mann-Whitney's rank test depending on distribution. Categorical variables were tested using χ^2 test or Fisher's exact test. A $3 \times 2 \chi^2$ test was employed to compare the three stages of CAN (none, early and definitive) between patients with SLE and controls. Multivariable linear and logistic regression analyses were used to perform adjusted groupwise comparisons. SPSS Statistics,

V.22 (IBM, SPSS, Chicago, Illinois, USA) was used. Statistical significance was defined as $p < 0.05$.

RESULTS

Of 111 patients with SLE, 92 answered PROMs, and 55 were matched 1:1 to controls. Characteristics of all subjects are presented in table 1. PROM patients were similar to the remaining patients (n=19). Matched patients were older, had a higher weight and BMI, lower hip/waist ratio and SDI score than the remaining patients (n=56).

Cumulative clinical SLE manifestations according to the ACR SLE classification criteria in the 111 patients with SLE comprised malar rash (59%), discoid rash (13%), photo sensitivity (41%), oral ulcers (25%), arthritis (72%), serositis (42%), renal disorder (60%), neurologic disorder (8.1%), haematological disorder (79%),

Table 1 Characteristics of the included patients with SLE and healthy controls (HCs)

	All patients with SLE	SLE with PROM	SLE matched to HC	HC	P value*	P value†	P value‡
Demographics							
Subjects, n (%)	111 (100)	92 (82.9)	55 (50)	55 (100)	–	–	–
Women, n (%)	99 (89.2)	82 (89.1)	47 (85.5)	47 (85.5)	1.00	0.24	–
Age, years, mean (SD)	51.5 (12.7)	50.9 (12.9)	57.6 (11.0)	58.0 (11.0)	0.32	0.001	–
Clinical examination, mean (SD)							
Height, cm	167.7 (7.1)	167.5 (7.2)	167.1 (8.4)	168.9 (7.6)	0.45	0.36	0.25
Weight, kg	70.7 (13.9)	70.1 (14.4)	74.3 (14.9)	71.7 (14.7)	0.39	0.006	0.36
BMI, kg/m ²	25.1 (5.0)	25.0 (5.2)	26.6 (5.2)	25.1 (4.2)	0.47	0.002	0.09
Hip/waist ratio	1.20 (0.12)	1.20 (0.11)	1.15 (0.12)	1.13 (0.07)	0.46	0.001	0.27
Mean arterial pressure, mm Hg	89.1 (12.3)	89.3 (13.4)	91.1 (12.4)	98.2 (12.5)	0.68	0.09	0.001
Heart rate, BPM	64.35 (10.7)	63.6 (12.5)	66.0 (10.8)	62.0 (9.8)	0.64	0.10	0.041
Smoking and medication, n (%)							
Current smoking	15 (13.5)	13 (14.1)	8 (14.5)	26 (47.3)	0.87	0.87	0.001
Diuretics	26 (26.1)	26 (28.3)	15 (27.3)	6 (10.9)	0.39	0.79	0.05
Beta blockers	15 (13.5)	14 (15.2)	5 (9.1)	3 (5.5)	0.46	0.27	0.72
Calcium antagonists	14 (12.6)	12 (13.0)	9 (16.4)	5 (9.1)	1.00	0.27	0.39
ACE inhibitors	29 (26.1)	25 (27.2)	12 (21.8)	3 (5.5)	0.80	0.31	0.024
AngII-R antagonists	10 (9.0)	7 (7.6)	7 (12.7)	2 (3.6)	0.37	0.20	0.16
SLE characteristics							
Disease duration, years, mean (SD)	19.9 (9.5)	19.5 (9.8)	20.8 (10)	–	0.68	0.31	–
SLEDAI score, median (IQR)	3 (1-4)	4 (2-4)	2 (2-4)	–	0.05	0.08	–
SDI score, median (IQR)	2 (1-4)	2 (1-4)	1 (0-3)	–	0.12	0.05	–

*SLE patients with PROMs versus rest of patients.

†Matched patients with SLE versus rest of patients.

‡Matched patients with SLE versus HCs. For all comparisons, values in bold are considered significant ($p < 0.05$), AngII-R, angiotensin-II receptor; BMI, body mass index; HC, healthy control; PROM, patient-reported outcome measure; SDI, SLICC Damage Index; SLEDAI, SLE Disease Activity Index.

Table 2 Variables reflecting autonomic nervous system function in patients with SLE and healthy controls (HCs) matched by age and sex

	SLE (n=54)	HC (n=54)	P value
HRV indices, median (IQR)*			
SDNN, ms	28.3 (21.1–37.9)	36.7 (28.5–53.4)	0.019
RMSSD, ms	18.3 (8.8–27.0)	25.7 (18.4–38.0)	0.007
LF, ms ²	61.0 (33.3–129)	77.0 (48.8–185)	0.08
HF, ms ²	34.8 (10.6–73.0)	84.3 (33.4–198)	<0.001
TP, ms ²	215 (125–445)	373 (213–788)	0.011
LF/HF ratio	2.05 (1.03–3.94)	1.02 (0.44–2.37)	0.001
CARTs, median (IQR)*			
RS ratio	1.08 (1.01–1.14)	1.26 (1.14–1.35)	<0.001
EI ratio	1.15 (1.09–1.28)	1.22 (1.11–1.32)	0.042
VM ratio	1.45 (1.24–1.60)	1.63 (1.47–1.80)	<0.001
CAN stage, n (%)			
No CAN	25 (46.3)	42 (77.8)	0.001
Early CAN	16 (29.6)	11 (20.4)	
Definitive CAN	13 (24.1)	1 (1.9)	

*Natural logarithm applied for parametric analyses. Values in bold are considered significant ($p < 0.05$).

CAN, cardiovascular autonomic neuropathy; CARTs, cardiovascular autonomic reflex tests; EI, expiration/inspiration; HF, high frequency power; HRV, heart rate variability; LF, low frequency power; RMSSD, root mean square of successive differences between normal heartbeats; RS, response to standing; SDNN, SD of all NN intervals; TP, total power; VM, Valsalva manoeuvre.

immunological disorder (86%) and ANA (100%). The matched SLE patients and controls were similar in most characteristics, but differed in resting heart rate, mean arterial pressure (MAP), smoking and ACE inhibitors.

Prevalence of autonomic dysfunction in SLE versus healthy controls

Among the 109 patients with SLE completing at least two CARTs, the definitive CAN prevalence was 24.8%, whereas 57.8% presented with either definitive or early CAN. Patients with SLE had significantly lower HRV, CART scores and more patients had definitive CAN than controls (table 2). Fifty-four patients with SLE (and 54 controls) completed the RS test, 55 (54 controls) completed the EI test and 42 (46 controls) completed the VM test. One SLE and one control subject only completed one CART and was not CAN classified. The SLE group had significantly lower CARTs than controls (RS ratio: 14.3%, EI ratio: 5.7% and VM ratio: 11.1%, table 2). Accordingly, the prevalence of definitive CAN in SLE was 24.1% (95% CI 15% to 37%), compared with 1.9% (one subject; 95% CI 0.3% to 9.8%) in the controls, and the subsequent OR was 16.8 (95% CI 2.1 to 133.8, $p = 0.008$). Furthermore, the prevalence of any CAN (early+definitive) was 53.7% (95% CI 41% to 66%) in patients with SLE versus 22.6% (95% CI 13% to 35%) in the control group (OR 4.06, 95% CI 1.76 to 9.36, $p = 0.001$).

In each group, 54 subjects performed the 5 min passive HRV test. The two HRV indices reflecting PNS modulation (RMSSD, HF power) were lower in patients with SLE. Furthermore, some indices of mixed PNS and SNS

modulation were significantly lower (SDNN and TP) or higher (LF/HF ratio) in patients with SLE (table 2).

The associations presented in table 2 were also adjusted for MAP, resting heart rate, usage of ACE inhibitor and smoking status as presented in online supplemental table S1. Adjusting for MAP, usage of ACE inhibitors and smoking status did overall not change the results. When adjusting for resting heart rate, the HRV indices (HF and LF/HF ratio), CARTs (RS and VM ratio) and CAN staging of the patients still differed from controls.

Resting heart rate was only associated to impaired autonomic function in the SLE group (lower SDNN, RMSSD, LF, HF, TP and RS ratio and higher LF/HF ratio and CAN stage: all $|Rho| \geq 0.30$, $p < 0.05$) and not in controls (all $|rho| \leq 0.24$, $p > 0.05$).

Autonomic function in SLE patients without and with CAN

SLE patients with no CAN presented with altered autonomic modulation compared with controls (table 3). Two CART medians, reflecting mixed SNS-PNS activity, were significantly lower in the no CAN SLE group compared with the no CAN controls (table 3). Further, HF-power, reflecting PNS modulation, was significantly lower in SLE without CAN compared with similar controls. Conversely, of the mixed PNS-SNS modulation indices only the LF/HF ratio was higher in SLE. Patients and controls without CAN only differed in subject characteristics by MAP (SLE: 88.7 ± 10.7 vs controls 96.8 ± 11.8 (mean \pm SD), $p = 0.006$). Adjusting autonomic group differences with MAP, only HF remained significantly lower in the SLE group ($p = 0.046$).

Table 3 Variables reflecting autonomic nervous system function in patients with SLE and healthy controls (HCs) without cardiovascular autonomic neuropathy (CAN), matched by age and sex

	HC with no CAN (n=41)	SLE with no CAN (n=25)	P value*	P value†
HRV indices, median (IQR)				
SDNN, ms	38.3 (30.9–58.1)	33.9 (25.5–44.3)	0.21	0.53
RMSSD, ms	29.4 (19.0–39.8)	20.8 (14.6–40.9)	0.19	0.60
LF, ms ²	108 (52.9–288)	79.8 (45.8–192)	0.88	0.83
HF, ms ²	97.7 (47.1–237)	53.7 (22.6–101)	0.040	0.046
TP, ms ²	442 (232–1037)	331 (162–516)	0.22	0.20
LF/HF ratio	0.79 (0.40–2.37)	1.70 (0.78–3.56)	0.049	0.09
CARTs, median (IQR)				
RS ratio	1.25 (1.16–1.38)	1.10 (1.07–1.19)	<0.001	0.001
EI ratio	1.24 (1.16–1.33)	1.21 (1.15–1.28)	0.12	0.09
VM ratio	1.63 (1.54–1.81)	1.52 (1.37–1.70)	0.019	0.022

*Unadjusted analysis.

†Logistic regression analysis adjusted for mean arterial pressure. For all analyses, the dependent variables were logarithmically transformed and values in bold are considered significant ($p < 0.05$).

EI, expiration/inspiration; HF, high frequency power; HRV, heart rate variability; LF, low frequency power; RMSSD, root mean square of successive differences between normal heartbeats; RS, response to standing; SDNN, SD of all NN intervals; TP, total power; VM, Valsalva manoeuvre.

Extending these observations into SLE patients with definitive CAN by comparison with patients without CAN, aberrant ANS characteristics similarly involved impaired modulation of PNS activity (RMSSD, HF power) but now also of mixed SNS-PNS activity (SDNN, LF power, TP, all $p < 0.05$). Definitive CAN patients presented with the following HRV values by median (IQR): SDNN: 20.9 (16.0–35.8), RMSSD: 36.4 (10.3–66.8) and LF: 5.2 (51.0–262.5). The only ANS variable not different from SLE patients without CAN was the HF/LF ratio (median: 2.94, IQR: 1.41–8.37, $p = 0.114$).

Autonomic function and HRQoL in SLE

The physical component score for the 92 patients with SLE completing the SF-12 questionnaire was 44.2 ± 10.5 , whereas the mental component score was 47.8 ± 9.9 . Low physical component scores were associated with measures of impaired autonomic function (table 4). Specifically, lower physical component scores were associated with indices of impaired PNS modulation (by low RMSSD and HF power), impaired mixed PNS/SNS modulation (by low SDNN, TP and RS ratio) and presence of definitive CAN. No associations were observed between the SF-12 mental component scores and any ANS indices.

DISCUSSION

In this study, we reproduce previous findings of an increased prevalence of CAN in patients with SLE. As a new finding, this study shows that the type of autonomic dysfunction in these patients depends on the severity of CAN. SLE patients without CAN presented with impaired parasympathetic activity, whereas SLE patients with definitive CAN also showed signs of mixed sympathetic/

parasympathetic dysfunction. Moreover, SLE patients with impairment of parasympathetic as well as mixed sympathetic/parasympathetic activity reported lower HRQoL scores in the physical component of the SF-12 questionnaire.

The prevalence of definitive CAN in this study was 24.1% in the matched patients with SLE, 1.9% in the controls and 24.8% in the 109 patients with SLE. This and the prevalence of early CAN could be underestimated as not all subjects completed all three CARTs necessary for CAN staging. However, the number of subjects not completing all tests were equally distributed in the two groups.

In previous studies, the prevalence of CART-based CAN has ranged from 23.5% to 82.7%, proposedly caused by methodological inconsistency, unstandardised test conditions and varying age of the studied populations.² Two authors, Stojanovich *et al*⁹ and Milovanovic *et al*,³² report on two SLE populations, resembling ours by age, and reported higher CAN prevalences (79.6% and 82.7%) than in the current study. Like in the current study, both authors considered CAN present when two or more of the CARTs were abnormal. However, our subjects performed fewer CARTs (three) than those of Stojanovic *et al* and Milovanovic *et al* (five and four, respectively). Furthermore, recommended age dependent cut-off values⁴ was applied only in this study. Hence, the method used by our colleagues may be more sensitive, however also less specific, as indicated by CAN prevalence estimates in control subjects ranging from 11.4% to 43.6% versus 1.9% in our study.

A recent review on SLE and HRV report that patients with SLE consistently present with lower HRV compared

Table 4 Health-related quality of life and autonomic nervous system function

	SF-12 PCS		SF-12 MCS		Age, years	
	β	P value	β	P value	β	P value
HRV indices*						
SDNN, ln(ms)	0.257	0.014	-0.092	0.35	-0.250	0.016
RMSSD, ln(ms)	0.211	0.043	-0.045	0.65	-0.297	0.004
LF, ln(ms ²)	0.181	0.08	-0.151	0.13	-0.293	0.005
HF, ln(ms ²)	0.216	0.029	-0.060	0.52	-0.390	0.001
TP, ln(ms ²)	0.276	0.008	-0.097	0.33	-0.248	0.016
LF/HF ratio, ln	-0.090	0.41	-0.120	0.25	0.211	0.05
CARTs*						
RS ratio, ln	0.225	0.018	-0.116	0.20	-0.443	<0.001
EI ratio, ln	0.163	0.12	-0.105	0.30	-0.304	0.004
VM ratio, ln	0.081	0.53	0.114	0.35	-0.187	0.15
CAN stages†						
eCAN (n=32):noCAN (n=39)	-0.068	0.52	0.029	0.79	0.129	0.21
dCAN (n=24):noCAN (n=39)	-0.220	0.033	0.065	0.52	0.091	0.36

Age-controlled associations between SF-12 physical (PCS) and mental (MCS) component scores and measures of autonomic nervous system function in 92 patients with SLE.

*Multivariable regression analyses.

†Logistic multivariable regression analyses; values in bold are considered significant ($p < 0.05$).

β , regression coefficient standardised by corresponding SD; CARTs, cardiovascular autonomic reflex tests; dCAN, definitive cardiovascular autonomic neuropathy (CAN); eCAN, early CAN; HF, high frequency power; HRV, heart rate variability; LF, low frequency power; noCAN, no CAN; RMSSD, root mean square of successive differences between normal heartbeats; TP, total power.

with controls,¹ corresponding to our findings: patients with SLE presented with lower variability in all items except LF power, whereas the LF/HF ratio was increased. The LF band reflects both PNS and SNS activity,²¹ whereas higher values of LF/HF may reflect sympathetic predominance.²² Thus, in accordance with previous findings,¹ our results indicate that the parasympathetic and to some extent the sympathetic activities are impaired in SLE, with a relative sympathetic predominance.

As the ANS is highly adaptive to its environment, it is recommended to minimise the influence of confounders to increase the reliability of ANS tests.^{4 26} However, adjusting for differences in baseline MAP, smoking status and ACE inhibitor in the SLE control comparison did not change our results. When adjusting for heart rate, the association between SLE and especially mixed SNS-PNS activity was less pronounced. However, the argument for these adjustments is debatable since resting heart rate was elevated in patients with SLE and associated with autonomic function in the patients only thereby inferring risk of over adjustment. Hence, it seems likely that patients with SLE presented with impaired autonomic activity associated with SLE disease properties, despite differences in potential confounders compared with controls.

To our knowledge, only two studies have investigated SLE patients with CARTs and HRV concurrently.^{32 33} However, no previous SLE studies have previously investigated HRV in patients without CAN. Doing this, results suggesting that even patients with no evident

CARTs-determined CAN have impaired HRV compared with similar controls. As HRV is a more sensitive marker of ANS dysfunction than reflex test scores,^{34 35} our findings may imply that SLE patients with a seemingly well-functioning ANS may show signs of incipient autonomic dysfunction, possibly increasing the risk of developing CAN. However, based on our cross-sectional design, this remains to be confirmed in prospective SLE studies.

The potential incipient CAN was characterised by low PNS function (based on HF) with a sympathetic predominance (based on high LF/HF ratio), probably based on the impaired parasympathetic activity rather than increased sympathetic activity. Definitive CAN was, in addition to impaired PNS activity (based on RMSSD and HF power), further characterised by HRV impairments reflecting both SNS and PNS dysfunction (SDNN, LF power, TP). Hence, it seems that involvement of both the parasympathetic and, perhaps, especially the sympathetic nervous system characterises late CAN in SLE. Altogether, this may indicate that, in SLE, dysfunction of the PNS precedes the SNS and the presentation with definitive CAN. Similar progression was suggested in diabetes,³⁶ while other suggest simultaneous PNS and SNS impairment.³⁷ Clinically, another important finding was the association between ANS dysfunction and self-report of low physical HRQoL. Self-perceived physical health evaluated by the physical component score of SF12 comprises perception of general health, physical function, capacity to perform physical activities compared

with the subjectively expected capacity and the influence of pain on daily work.²⁹

The perception of low physical HRQoL was associated with measures reflecting PNS impairment (RMSSD and HF) and mixed ANS impairment (LF power, TP and definitive CAN). Hence, this finding suggests that both early and extensive/late CAN may contribute to self-perceived low physical health, function, capacity and elevated pain in patients with SLE. Whereas the relationship between autonomic function and physical HRQoL has not previously been investigated in SLE, similar results were found in healthy subjects¹² and patients with end-stage renal disease,¹⁵ paroxysmal atrial fibrillation,¹³ chronic obstructive pulmonary disease,¹⁴ Parkinson's disease³⁸ and diabetes.³⁹ Furthermore, this association in SLE is supported by the recent pilot study in which 12 days of PNS stimulation led to decreased experience of pain and fatigue.¹⁰

We speculate that altered autonomic function may affect physical HRQoL in SLE by: (1) altered perception due to reduced psychological resiliency,²² (2) symptoms of autonomic dysfunction, which in diabetes are considered late complications of CAN⁴ or (3) by interaction with SLE-related disease mechanisms such as inflammation, autoantibody production, neuropsychiatric and cardiovascular comorbidities.⁶⁻⁹

Whereas physical HRQoL was associated to impaired autonomic function in the current study, mental HRQoL was not. In non-SLE populations, impaired ANS function has been implicated in psychiatric diseases with impaired mental HRQoL.⁴⁰⁻⁴¹ Patients with SLE experience a high level of neuropsychiatric disorders like depression and anxiety, of which both are strong independent predictors of low level of HRQoL.⁴² Therefore, we hypothesise that the subjective symptoms of impaired mental health is stronger associated to the SLE disease itself than ANS function. However, this was not investigated currently.

The present study has some limitations. First, due to the cross-sectional design, causality of the observed associations regarding the natural course of autonomic dysfunction in SLE and the association between autonomic dysfunction and HRQoL cannot be inferred. Furthermore, none of the currently included measures of ANS function were influenced solely by sympathetic modulation. The most specific measures of sympathetic function include blood pressure CARTs,⁴³ and these could yield new sympathetic characteristics of the autonomic dysfunction present in SLE. However, these were not included in this study. Despite evident limitations, this study has been the first to explore early signs of autonomic dysfunction in SLE by associating CART-based CAN staging with HRV analyses. Furthermore, this is the first study to provide insight to how ANS dysfunction may influence physical signs of SLE from a patient perspective. The study findings may, if validated in prospective studies, prove clinically useful by providing an alternative understanding of poor HRQoL that is not readily explained by known disease characteristics of SLE.

In conclusion, we found that compared with controls, patients with SLE presented more frequently with CAN characterised by mixed parasympathetic/sympathetic impairment. Furthermore, even in patients without clinical signs of CAN, we demonstrated impaired parasympathetic function. These impairments were in patients with SLE associated with self-report of poor physical quality of life.

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Contributors AHZ designed the trial and the data collection tools, wrote the statistical analysis plan, monitored the data collection for the whole trial, cleaned, analysed and interpreted the data and drafted the paper. KKI and HCBL monitored the data collection, analysed and interpreted data in the PLUSheart study. EL and JF monitored the data collection, analysed and interpreted data in the IMPACT study. SJ designed the trial, wrote the statistical analysis plan, monitored the data collection for the whole trial, and analysed and interpreted the data. All authors revised the paper.

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Competing interests JF is the coinventor of the Vagus device.

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Table S1: Estimations of association between SLE (n=54) and autonomic nervous system variables using healthy subjects (n=54) as reference by unadjusted and adjusted logistic regression analyses.

	Unadjusted		Adjusted for MAP		Adjusted for HR		Adjusted for smoking status		Adjusted for ACE-inhibitor	
	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
HRV indices										
SDNN, ln(ms)	0.41 (0.19-0.88)	0.023	0.40 (0.17-0.92)	0.031	0.48 (0.21-1.09)	0.08	0.43 (0.19-0.94)	0.034	0.46 (0.21-0.98)	0.045
RMSSD, ln(ms)	0.51 (0.31-0.85)	0.009	0.45 (0.25-0.79)	0.006	0.58 (0.33-1.01)	0.05	0.52 (0.31-0.88)	0.015	0.54 (0.32-0.90)	0.018
LF, ln(ms ²)	0.76 (0.55-1.04)	0.08	0.71 (0.50-1.01)	0.06	0.85 (0.60-1.20)	0.34	0.78 (0.56-1.09)	0.14	0.76 (0.55-1.05)	0.10
HF, ln(ms ²)	0.60 (0.45-0.81)	0.001	0.53 (0.37-0.74)	<0.001	0.63 (0.46-0.86)	0.004	0.62 (0.46-0.83)	0.002	0.63 (0.47-0.84)	0.002
TP, ln(ms ²)	0.63 (0.44-0.91)	0.014	0.58 (0.39-0.88)	0.010	0.69 (0.46-1.02)	0.063	0.65 (0.45-0.97)	0.032	0.66 (0.46-0.96)	0.030
LF/HF-ratio, ln	1.90 (1.27-2.29)	0.002	2.12 (1.35-3.33)	0.001	1.83 (1.21-2.76)	0.004	1.89 (1.24-2.88)	0.003	1.78 (1.17-2.70)	0.007
CARTs										
RS-ratio, ln	0.00 (0.00-0.01)	<0.001	0.00 (0.00-0.00)	<0.001	0.00 (0.00-0.00)	<0.001	0.00 (0.00-0.01)	<0.001	0.00 (0.00-0.01)	<0.001
EI-ratio, ln	0.03 (0.01-0.92)	0.045	0.01 (0.00-0.25)	0.009	0.03 (0.01-1.09)	0.05	0.03 (0.01-1.04)	0.05	0.03 (0.00-1.26)	0.07
VM-ratio, ln	0.01 (0.00-0.14)	0.001	0.00 (0.00-0.08)	0.001	0.01 (0.01-0.22)	0.003	0.01 (0.00-0.17)	0.002	0.07 (0.00-0.14)	0.001
CAN stage	3.34 (1.76-6.58)	<0.001	4.61 (2.15-9.87)	<0.001	3.14 (1.59-6.20)	0.001	3.57 (1.72-7.38)	0.001	3.34 (1.70-6.79)	0.001

MAP: Mean arterial pressure; HR: Heart rate; ACE: Angiotensin converting enzyme; OR: Odds ratio; CI: Confidence interval; HRV: Heart rate variability; SDNN: Standard deviation of all NN-intervals; RMSSD: Root mean square of successive differences between normal heartbeats; LF: Low frequency power; HF: High frequency power; TP: Total power; CARTs: cardiovascular autonomic reflex tests; RS: Response to standing; EI: Expiration/inspiration; VM: Valsalva maneuver; CAN: Cardiovascular autonomic neuropathy; For all comparisons p < 0.05 indicated statistical significance.