RHEUMATOLOGY

Original article

Cardiac magnetic resonance predicts ventricular arrhythmias in scleroderma: the Scleroderma Arrhythmia Clinical Utility Study (SAnCtUS)

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Abstract

Objectives. Cardiac rhythm disturbances constitute the most frequent cardiovascular cause of death in SSc. However, electrocardiographic findings are not a part of risk stratification in SSc. We aimed to translate 24 h Holter findings into a tangible risk prediction score using cardiovascular magnetic resonance.

Methods. The Scleroderma Arrhythmia Clinical Utility Study (SAnCtUS) was a prospective multicentre study including 150 consecutive SSc patients from eight European centres, assessed with 24 h Holter and cardiovascular magnetic resonance, including ventricular function, oedema (T2 ratio) and late gadolinium enhancement (%LGE). Laboratory/clinical parameters were included in multivariable corrections. A combined endpoint of sustained ventricular tachycardia requiring hospitalization and sudden cardiac death at a median (interquartile range) follow-up of 1 (1.0–1.4) year was generated.

Results. Only T2 ratio and %LGE were significant predictors of ventricular rhythm disturbances, but not of supraventricular rhythm disturbances, after multivariable correction and adjustment for multiple comparisons. Using decision-tree analysis, we created the SAnCtUS score, a four-category scoring system based on T2 ratio and %LGE, for identifying SSc patients at high risk of experiencing ventricular rhythm disturbance at baseline. Increasing SAnCtUS scores were associated with a greater disease and arrhythmic burden. All cases of non-sustained ventricular tachycardia ($n = 7$) occurred in patients with the highest SAnCtUS score (=4). Having a score of 4 conveyed a higher risk of reaching the combined endpoint in multivariable Cox regression compared with scores 1/2/3 [hazard ratio (95% CI): 3.86 (1.14, 13.04), $P = 0.029$] independently of left ventricular ejection fraction and baseline ventricular tachycardia occurrence.

Conclusion. T2 ratio and %LGE had the greatest utility as independent predictors of rhythm disturbances in SSc patients.

Key words: scleroderma, systemic sclerosis, cardiovascular magnetic resonance, sudden cardiac death, rhythm disturbance

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CLINICAL SCIENCE

Rheumatology key messages

- Cardiac rhythm disturbances are the most frequent cause of death SSc.
- T2 ratio and late gadolinium enhancement had the greatest utility as independent predictors of cardiac rhythm disturbances in SSc.

Introduction

SSc is an autoimmune disease leading to microvascular damage and fibrosis of the skin and internal organs [1]. SSc affects ~2.5 million patients worldwide with 300 000 new cases being diagnosed per year [2], and studies place cardiac-related mortality between 26 and 36% [3, 4]. Rhythm disturbances account for the majority of cardiac death, and cardiac involvement conveys a poorer prognosis in SSc [3, 5], with the 24 h Holter recording constituting the mainstay of initial cardiac evaluation [6]. The incidence of sudden cardiac death (SCD) in SSc may be underestimated in the literature [7], as it has not been recently evaluated by large studies and the causes of death in SSc have changed over the years in response to newer therapeutic approaches [8].

The Scleroderma Clinical Trial Consortium emphasized that cardiac rhythm disturbances are frequent in SSc and negatively affect prognosis [9]. Thus, implantable cardioverter defibrillator (ICD) implantation in SSc patients may prevent SCD [10]. Although clear guidelines/indications for ICD implantation exist for conditions such as sarcoidosis, myotonic dystrophy and Chagas disease, no such guidelines exist for SSc [1, 9, 11]. Thus, the decision for ICD implantation must abide by criteria established for non-ischaemic cardiomyopathies, a prerequisite of which is a left ventricular ejection fraction (LVEF) $\leqslant 35\%$ [9], which by itself is neither sensitive nor specific [12]. In addition, SCD in SSc patients is due to myocardial fibrosis, which may occur in the absence of reduced LVEF and is present in 12–80% of patients at autopsy [13–15]. Despite being the initial investigation of choice, any diagnostic information contained in 24 h Holter recordings is not utilized when considering ICD implantation. This is mainly because no electrocardiographic parameter adequately stratifies oligo-asymptomatic patients with regard to SCD risk [9], which makes the interpretation of 24 h Holter findings challenging. Furthermore, the diagnostic efficacy of Holter recordings is high only in patients exhibiting rhythm disturbances during the recording [16], and sustained ventricular tachycardia (VT) occurs asymptomatically in up to 50% of patients [17].

The aforementioned issues indicate a need for reconsideration of the currently employed anti-arrhythmic strategies, as well as inclusion of disease parameters other than LVEF in decision-making algorithms and ICD implantation indications. Cardiovascular magnetic resonance (CMR) offers considerable additional utility beyond LVEF in SSc by allowing the identification of myocardial oedema and fibrosis [18, 19], as myocardial fibrosis is the most common substrate for re-entrant arrhythmias [20]. CMR can thus potentially translate 24 h Holter findings to distinguishable structural myocardial abnormalities functioning as arrhythmogenic foci, as myocardial fibrosis identified by CMR is the most common arrhythmogenic substrate specifically in non-ischaemic cardiomyopathies [21, 22], and larger scar extents are associated with increased risk of inducible VT or SCD [22]. We hypothesized that CMR indices would be independently associated with the occurrence of rhythm disturbances and SCD in SSc patients. Our aim was to evaluate a population of consecutive SSc patients with suspected cardiac involvement using 24 h Holter recordings and CMR. By identifying CMR indices that optimally predict rhythm disturbances identified at baseline 24 h Holter recordings, we aimed to generate and calibrate a risk score that could predict future life-threatening rhythm disturbances in SSc patients better than currently employed methods. To address our aims, we organized and carried out the Scleroderma Arrhythmia Clinical Utility Study (SAnCtUS).

Methods

Patients

SAnCtUS was a multicentre, prospective, longitudinal study that included SSc patients classified according to the ACR/EULAR criteria and divided into lcSSc/dcSSc subsets [23]. Between 2010 and 2016, consecutive SSc patients were prospectively recruited and evaluated with 24 h Holter recordings and CMR within 10–60 days after the Holter assessment. Participants were referred for CMR either for evaluation of cardiovascular symptoms or events, or in the context of locally instituted screening programmes for primary prevention of SSc-related cardiac involvement. Cardiovascular indications included typical or atypical chest pain, shortness of breath and/or palpitations, as well as clinically documented occurrences of supraventricular or ventricular rhythm disturbances and/or syncope. Patients with signs or symptoms of concomitant myositis and contraindications to CMR (allergy to paramagnetic contrast agents, severe renal failure, non-CMR-conditional devices or implanted metals) were excluded from the study.

SAnCtUS combined data from eight European clinical research centres, namely the Azienda University Hospital (Florence, Italy), the Institute of Clinical Physiology, National Research Council (Pisa, Italy), the G. Monasterio C.N.R. – Regione Toscana Foundation (Pisa, Italy), the Humanitas Clinical and Research Center (Milan, Italy), the Laikon University Hospital, Onassis Cardiac Surgery Center and Athens Naval Hospital (Athens, Greece), and the Aristotle University Hospital of Thessaloniki (Thessaloniki, Greece). Prior approval of local medical ethics committees was obtained and participants provided written informed consent. Available descriptive parameters were age, sex, medication, presence of anti-topoisomerase I antibodies and specifically in lcSSc patients the presence of ACAs, New York Heart Association functional class and modified Rodnan

skin score for skin involvement (0 normal, 1–14 mild, 15–29 moderate, 30–39 severe, 40+ end-stage) [24]. At one year after CMR/24 h Holter evaluation, participants were followed-up for sustained VT occurrence and physician-adjudicated cardiac-related hospitalization or death; a combined endpoint was generated from the aforementioned events. Median follow-up duration was 1 year (interquartile range: 1–1.4 years) and results were censored at the one-year timepoint.

CMR data analysis

CMR evaluation included assessment of left and right ventricular function, oedema (T2 ratio) and replacement fibrosis [late gadolinium enhancement (%LGE)]. All CMR data acquisition methods are described in detail in the supplementary material, section Supplementary Methods, available at *Rheumatology* online.

Analysis of 24 h Holter recordings

The 24 h Holter data were obtained from all included patients and were analysed by three independent observers (S.M., L.G. and K.B.) blinded to clinical and CMR data, according to criteria used in similar SSc studies [25]. The 24 h Holter data were analysed collectively as supraventricular, ventricular or any rhythm disturbances as follows:

- Supraventricular rhythm disturbances:
  - Atrioventricular block
  - Atrial fibrillation
  - Run of paroxysmal supraventricular tachycardia
- Ventricular rhythm disturbances:
  - Any presence of premature ventricular contractions (PVCs)
  - Polymorphic PVCs
  - PVCs in couples
  - PVCs in triplets
  - Bigeminy/trigeminy/quadrigeminy
  - Run of non-sustained VT [three or more consecutive beats arising below the atrioventricular node with an RR interval of <600 ms (>100 beats/min) and lasting <30 s] [26]
  - Run of sustained VT [a series of consecutive PVCs (⩾120 beats/min) and lasting >30 s] [27]

Statistical analysis

Basic methodology

The software Stata SE v.15 (StataCorp LLC, College Station, TX, USA) was used for statistical analyses. Normality of continuous variables was determined by visual assessment of Q-Q plots or histograms. Normally distributed continuous variables are presented as mean (s.d.), not-normally distributed continuous variables are presented as median (interquartile range) and categorical variables are presented as number (%). Statistical significance was considered for $P \leqslant 0.05$. For multiple statistical comparisons, a Benjamini–Hochberg correction was used to determine statistical significance (false discovery rate 0.05) [28].

Statistical comparisons

Chained multiple imputation was used for obtaining values of missing data. All CMR variables were investigated as predictors of the occurrence of baseline cardiac rhythm disturbances with univariable logistic regression analysis across all imputation iterations. Rhythm disturbances classified into 'supraventricular', 'ventricular' and 'any type' groups, as defined previously, were used as dependent variables. Multivariable corrections were subsequently performed for age and disease duration at study inclusion, seropositivity for anti-topoisomerase I antibody, dcSSc *vs* lcSSc subset and modified Rodnan skin score. After identifying independent CMR predictors of baseline rhythm disturbances based on imputed values, a decision-tree algorithm was used to optimally classify only non-imputed data ($n = 129$) into clinically meaningful clusters based on the prediction of the occurrence of ventricular rhythm disturbances at baseline. These were used to generate the SAnCtUS score, which was subsequently compared with LVEF and the occurrence of VT at baseline as predictors of the combined endpoint at 1-year follow-up using multivariable Cox regression. A random forest approach was used as a sensitivity analysis and to ensure external validity. All statistical procedures are discussed in greater detail in the supplementary material, section Supplementary Methods, available at *Rheumatology* online.

Results

The study population consisted of 150 patients aged 54.3 ± 13.8 years, with 126 (84%) being female, 79 (53.4%) having cardiovascular symptoms or events at inclusion and 89 (59.3%) having dcSSc. In total, 108 (73.4%), 128 (87.1%) and 36 (24.5%) used immunomodulatory, cardiovascular and anti-platelet medication, respectively. Median LVEF was 64.5 (61.0–69.7), with eight (5.3%) patients having an LVEF <50% and two (1.3%) patients having an LVEF ⩽35%. Seventy-three (48.7%) patients experienced one or more rhythm disturbances of any type, with 20 (13.3%) having at least one type of supraventricular rhythm disturbance and 68 (45.3%) at least one type of ventricular rhythm disturbance. A single patient had atrioventricular block, with another having pulmonary hypertension (0.7% for both). Descriptive statistics including the relative frequencies of all rhythm disturbances are presented in Table 1. The results of logistic regression analyses are presented in Table 2. Odds ratios (OR) and 95% CI presented for T2 ratio are adjusted for a 0.1 unit change.

Supraventricular rhythm disturbances

In univariable analyses only T2 ratio and %LGE were significant predictors of supraventricular rhythm disturbances. After multivariable corrections, right ventricular ejection fraction, T2 ratio and %LGE were significant predictors. However, after correction for multiple comparisons, only %LGE remained a significant univariable predictor [OR (95% CI): 1.11 (1.06, 1.22), $P < 0.001$], but

TABLE 1 Baseline characteristics for the entire patient cohort and per SAnCtUS score category

Variable	Whole cohort	SAnCtUS score				P-value
		1	2	3	4	
Number of patients	150	37	16	38	38	N/A
Demographics and laboratory, history and clinical parameters						
Sex (female), n (%)	126 (84.0)	31 (84)	14 (88)	30 (79)	31 (82)	0.88
Age (years)	54.3 (13.8)	56.8 (14.3)	50.3 (18.8)	50.9 (12.2)	55.4 (10.7)	0.16
Disease duration at study inclusion (years)	9.0 (6.0, 12.0)	7.0 (6.0, 10.0)	11.0 (7.0, 17.0)	10.5 (8.0, 15.0)	8.0 (4.0, 11.0)	0.020*
dcSSc, n (%)	89 (59.3)	16 (43)	4 (25)	28 (74)	36 (95)	<0.001*
Seropositive for ATA, n (%)	90 (60.4)	16 (43)	7 (47)	26 (68)	32 (84)	0.001*
Seropositive for ACA (lcSSc only), n (%)	18 (40)	6 (38)	5 (45)	2 (29)	0 (0)	0.77
Modified Rodnan skin score	4.0 (2.0, 8.0)	4.0 (0.0, 6.0)	2.0 (0.0, 7.0)	5.0 (3.0, 7.0)	5.0 (4.0, 17.0)	<0.001*
Modified Rodnan skin score (categories), n (%)						<0.001*
Normal	28 (20.0)	10 (29)	7 (47)	3 (8)	0 (0)	
Mild	87 (62.1)	21 (62)	8 (53)	30 (79)	24 (63)	
Moderate	24 (17.1)	3 (9)	0 (0)	5 (13)	13 (34)	
Severe	1 (0.7)	0 (0)	0 (0)	0 (0)	1 (3)	
NYHA functional class, n (%)						0.11
I	88 (58.7)	26 (70)	12 (75)	15 (39)	23 (61)	
II	51 (34.0)	9 (25)	4 (25)	19 (50)	13 (34)	
III	11 (7.3)	2 (5)	0 (0)	4 (11)	2 (5)	
IV	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
CMR variables						
LVEDV (ml/m^2)	88.0 (72.0, 126.0)	74.0 (65.0, 93.0)	73.0 (70.5, 83.0)	109.0 (88.0, 133.0)	128.3 (100.0, 138.0)	<0.001*
LVESV (ml/m^2)	33.0 (23.0, 46.0)	26.0 (20.0, 32.4)	25.4 (20.5, 27.5)	41.5 (34.0, 49.9)	44.5 (33.0, 70.0)	<0.001*
LVEF (%)	64.5 (61.0, 69.7)	67.0 (61.0, 71.0)	65.5 (63.0, 68.5)	64.0 (60.0, 69.0)	63.0 (51.0, 69.0)	0.096
LVEF <55%	19 (12.7)	1 (3)	1 (6)	4 (11)	10 (26)	0.014*
LVEF <50%	8 (5.3)	0 (0)	0 (0)	1 (3)	6 (16)	0.009*
LVEF ≤35%	2 (1.3)	0 (0)	0 (0)	0 (0)	2 (5)	0.182
LV mass	87.9 (74.0, 102.0)	88.0 (72.0, 104.2)	96.6 (86.3, 103.1)	84.5 (75.0, 96.5)	78.5 (71.0, 98.7)	0.080
RVEDV (ml/m^2)	86.5 (67.0, 119.0)	74.0 (65.0, 88.0)	76.8 (70.5, 84.0)	110.0 (83.0, 134.0)	119.5 (100.0, 152.0)	<0.001*
RVESV (ml/m^2)	33.0 (23.0, 50.0)	25.4 (20.0, 33.0)	29.0 (21.5, 34.5)	40.5 (32.0, 57.0)	47.5 (34.4, 77.0)	<0.001*
RVEF (%)	62.0 (56.0, 68.0)	67.0 (61.0, 70.0)	61.0 (58.5, 69.5)	61.9 (55.0, 66.0)	58.5 (48.0, 62.9)	<0.001*
T2 signal ratio	2.0 (0.5)	1.6 (0.2)	2.3 (0.4)	2.0 (0.4)	2.3 (0.4)	<0.001*
LGE (present/absent)	88 (59.9)	0 (0)	0 (0)	38 (100)	38 (100)	<0.001*
LGE (% of LV mass)	2.0 (0.0, 5.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	3.0 (2.0, 3.8)	8.0 (6.0, 14.0)	<0.001*

(continued)

TABLE 1 Continued

Variable	Whole cohort	SAnCtUS score				P-value
		1	2	3	4	
Clinically relevant 24 h Holter findings						
VRD, n (%)	68 (45.3)	4 (10)	5 (31)	18 (47)	35 (92)	**<0.001***
More than 30 PVCs per h, n (%)	33 (22.0)	0 (0)	2 (13)	6 (16)	23 (61)	**<0.001***
Polymorphic PVCs, n (%)	17 (11.3)	2 (5)	1 (6)	2 (5)	10 (26)	**0.010***
PVCs in couples, n (%)	45 (30.0)	3 (8)	4 (25)	14 (37)	20 (53)	**<0.001***
PVCs in triplets, n (%)	13 (8.7)	0 (0)	0 (0)	1 (3)	10 (26)	**<0.001***
Bigeminy/trigeminy/quadrigeminy, n (%)	25 (16.7)	0 (0)	1 (6)	6 (16)	18 (47)	**<0.001***
Run of VT, n (%)	7 (4.7)	0 (0)	0 (0)	0 (0)	7 (18)	**<0.001***
SVRD, n (%)	20 (13.3)	1 (3)	0 (0)	4 (11)	12 (32)	**<0.001***
Run of PSVT, n (%)	9 (6.0)	1 (3)	0 (0)	1 (3)	4 (11)	0.22
AF, n (%)	12 (8.0)	0 (0)	0 (0)	3 (8)	8 (21)	**0.006***
AVB, n (%)	1 (0.7)	0 (0)	0 (0)	0 (0)	1 (3)	0.49
Any type of rhythm disturbances, n (%)	73 (48.7)	5 (14)	5 (31)	19 (50)	36 (95)	**<0.001***
≥2 types of SVRD, n (%)	2 (1.3)	0 (0)	0 (0)	0 (0)	1 (3)	0.49
≥2 types of VRD, n (%)	38 (25.3)	1 (3)	2 (13)	6 (16)	26 (68)	**<0.001***
SVRD and VRD, n (%)	15 (10.0)	0 (0)	0 (0)	3 (8)	11 (29)	**<0.001***
Medication						
Immunomodulatory medication, n (%)	108 (73)	21 (57)	6 (40)	33 (87)	38 (100)	**<0.001***
CS, n (%)	70 (47.6)	15 (41)	4 (27)	24 (63)	22 (58)	**0.043***
CYC, n (%)	9 (6.1)	2 (5)	0 (0)	2 (5)	5 (13)	0.30
MMF, n (%)	9 (6.1)	2 (5)	0 (0)	4 (11)	2 (5)	0.51
MTX, n (%)	43 (29.3)	6 (16)	1 (7)	16 (42)	19 (50)	**0.001***
Azathioprine, n (%)	30 (20.4)	3 (8)	1 (7)	8 (21)	14 (37)	**0.009***
HCQ, n (%)	29 (19.7)	10 (27)	1 (7)	6 (16)	10 (26)	0.27
Rituximab, n (%)	2 (1.4)	2 (5)	0 (0)	0 (0)	0 (0)	0.17
Cardiovascular medication, n (%)	128 (87)	30 (81)	12 (80)	36 (95)	38 (100)	**0.014***
ACEi/ARB, n (%)	47 (32.0)	7 (19)	4 (27)	12 (32)	21 (55)	**0.008***
Mineralocorticoid receptor antagonist, n (%)	2 (1.4)	0 (0)	0 (0)	1 (3)	0 (0)	0.50
β-adrenoreceptor blocker, n (%)	14 (9.5)	5 (14)	1 (7)	2 (5)	4 (11)	0.64
Diuretics, n (%)	13 (8.8)	6 (16)	0 (0)	2 (5)	3 (8)	0.19
CCB (dihydropyridine), n (%)	65 (44.2)	14 (38)	7 (47)	15 (39)	23 (61)	0.18
CCB (non-dihydropyridine), n (%)	29 (19.7)	4 (11)	1 (7)	13 (34)	11 (29)	**0.031***
Statin, n (%)	21 (14.3)	4 (11)	1 (7)	6 (16)	8 (21)	0.48
Prostanoids, n (%)	25 (17.0)	8 (22)	2 (13)	3 (8)	1 (3)	0.058
Sildenafil, n (%)	12 (8.2)	2 (5)	1 (7)	4 (11)	4 (11)	0.82
Endothelin receptor antagonist, n (%)	1 (0.7)	5 (14)	2 (13)	5 (13)	1 (3)	0.34
Nitrates, n (%)	2 (1.4)	2 (5)	0 (0)	0 (0)	1 (3)	0.42
Anti-coagulation, n (%)	36 (24)	13 (35)	7 (47)	5 (13)	4 (11)	**0.004***

(continued)

TABLE 1 Continued

Variable	Whole cohort	SAnCtUS score				P-value
		1	2	3	4	
Acetylsalicylic acid, n (%)	16 (10.9)	7 (19)	5 (33)	5 (13)	3 (8)	0.12
Other anti-platelet drugs, n (%)	13 (8.8)	7 (19)	3 (20)	0 (0)	0 (0)	**0.001***
Vitamin-K antagonist, n (%)	16 (10.9)	1 (3)	0 (0)	0 (0)	0 (0)	0.48
Novel anti-coagulants, n (%)	3 (2.0)	1 (3)	0 (0)	0 (0)	1 (3)	0.70
Other						
Proton pump inhibitor, n (%)	89 (60.5)	21 (57)	9 (60)	24 (63)	27 (71)	0.63

Descriptive statistics reflect only available values, not values obtained from imputation. All variables were available in all participants except for modified Rodnan skin scores, T2 ratio, %LGE [10 (6.7%), 14 (9.3%) and 15 (10%) missing values, respectively] and ACA values [16/61 (26.2%) for lcSSc patients only]. Medication was not available for three (2%) patients. *P ⩽ 0.05; bold type indicates statistical significance. SAnCtUS: Scleroderma Arrhythmia Clinical Utility Study; ATA: anti-topoisomerase I antibodies; NYHA: New York Heart Association; CMR: cardiovascular magnetic resonance; LV/RV: left/right ventricular; EDV/ESV: end-diastolic/end-systolic volume; EF: ejection fraction; LGE: late gadolinium enhancement; VT: ventricular tachycardia; VRD: ventricular rhythm disturbance; SVRD: supraventricular rhythm disturbance; PVC: premature ventricular contraction; PSVT: paroxysmal supraventricular tachycardia; AF: atrial fibrillation; AVB: atrioventricular block; ACEi/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB: calcium channel blocker.

not after multivariable correction. No statistical interactions were identified between patients with supraventricular rhythm disturbances with or without ventricular rhythm disturbances for any CMR variable.

Ventricular rhythm disturbances

All right and left ventricular volumes as well as right ventricular ejection fraction, T2 ratio and %LGE were significant univariable predictors of ventricular rhythm disturbances. After multivariable correction, only left ventricular end systolic volume, right ventricular ejection fraction, T2 ratio and %LGE remained significant predictors. Finally, after correction for multiple testing, only T2 ratio and %LGE remained significant univariable and multivariable predictors [multivariable OR (95% CI): 1.11 (1.01, 1.22), $P = 0.024$; and 1.31 (1.10, 1.57), $P = 0.002$, respectively]. Similar to supraventricular rhythm disturbances, no statistical interactions were identified between patients with ventricular rhythm disturbances with or without supraventricular rhythm disturbances for any CMR variable.

Any type of rhythm disturbances

The same significant univariable predictors for ventricular rhythm disturbances also predicted any type of rhythm disturbance. Similarly, after multivariable correction and correction for multiple testing, only T2 ratio and %LGE remained significant predictors of any type of rhythm disturbances [multivariable OR (95% CI): 1.17 (1.05, 1.29), $P = 0.005$; and 1.37 (1.10, 1.70), $P = 0.005$, respectively].

### Decision-tree analysis and SAnCtUS score

Using baseline ventricular rhythm disturbances as an outcome, we executed two separate decision-tree algorithms to cluster patients into categories for the optimal prediction of these events. One algorithm incorporated only significant independent predictors of baseline ventricular rhythm disturbances identified from logistic regression analysis (T2 ratio and %LGE), the other incorporated all available CMR variables. However, both algorithms resulted in the same decision tree. Patients were classified into four separate clusters according to their T2 ratio and %LGE values. We identified clinically meaningful cut-off points for defining each cluster by using the mean of the minimum value of the leading cluster and the maximum value of the immediately preceding cluster, as described in the supplementary material, section Supplementary Methods, available at *Rheumatology* online. Based on these results we created the 'SAnCtUS score' for predicting ventricular rhythm disturbances in SSc patients (Fig. 1). A random forest procedure yielded %LGE, left ventricular end diastolic volume and T2 ratio as the top three most contributing predictors with Cramér's V-based fit metric values of 0.29, 0.37 and 0.38, respectively. The four clusters identified by the decision-tree algorithms were sequentially named SAnCtUS scores 1, 2, 3 and 4, with cluster 1 having the least likelihood of experiencing ventricular rhythm disturbances. The algorithms first made a distinction between %LGE = 0% and %LGE > 0%.

TABLE 2 Results of logistic regression for included CMR variables as predictors of supraventricular, ventricular and any type of rhythm disturbances

| CMR index | Supraventricular rhythm disturbance | | | | Ventricular rhythm disturbance | | | | Any type of rhythm disturbance | | | |
| | Univariable | | Multivariable | | Univariable | | Multivariable | | Univariable | | Multivariable | |
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
LVEDV	1.008 (0.995, 1.021)	0.212	1.000 (0.983, 1.017)	0.980	1.016 (1.005, 1.027)	**0.006****	0.013 (0.000, 0.027)	0.053	1.015 (1.004, 1.027)	**0.008****	1.010 (0.996, 1.024)	0.172
LVESV	1.004 (0.981, 1.028)	0.735	0.984 (0.953, 1.016)	0.323	1.032 (1.009, 1.056)	**0.007****	1.028 (1.001, 1.055)	0.040*	1.027 (1.004, 1.050)	0.021*	1.016 (0.990, 1.042)	0.230
LVEF	1.025 (0.967, 1.087)	0.407	1.065 (0.995, 1.139)	0.071	0.963 (0.923, 1.006)	0.088	0.970 (0.926, 1.016)	0.202	0.979 (0.938, 1.021)	0.311	0.991 (0.946, 1.038)	0.710
LV mass	0.977 (0.953, 1.001)	0.063	0.982 (0.957, 1.008)	0.175	1.001 (0.988, 1.014)	0.888	1.005 (0.991, 1.019)	0.517	1.000 (0.987, 1.014)	0.986	1.005 (0.991, 1.020)	0.494
RVEDV	1.001 (0.991, 1.011)	0.853	0.995 (0.983, 1.007)	0.408	1.013 (1.003, 1.023)	**0.013****	1.010 (0.999, 1.022)	0.084	1.011 (1.001, 1.022)	0.025*	1.006 (0.995, 1.018)	0.285
RVESV	0.996 (0.978, 1.014)	0.634	0.983 (0.960, 1.007)	0.166	1.021 (1.003, 1.040)	**0.021***	1.016 (0.996, 1.036)	0.112	1.017 (1.000, 1.035)	0.049*	1.008 (0.990, 1.027)	0.390
RVEF	1.025 (0.971, 1.082)	0.377	1.077 (1.006, 1.153)	0.034*	0.942 (0.902, 0.983)	**0.007****	0.954 (0.911, 0.999)	0.043*	0.953 (0.913, 0.994)	0.025*	0.971 (0.927, 1.017)	0.207
T2 ratio (per 0.1 unit change)	1.128 (1.015, 1.254)	0.025*	1.136 (1.008, 1.280)	0.037*	1.112 (1.017, 1.217)	**0.020****	1.114 (1.014, 1.224)	**0.024****	1.154 (1.046, 1.274)	**0.004*****	1.165 (1.048, 1.294)	**0.005****
LGE (per 1% of LV mass change)	1.132 (1.055, 1.215)	**<0.001****	1.109 (1.015, 1.212)	0.022*	1.328 (1.121, 1.574)	**0.001****	1.314 (1.102, 1.566)	**0.002****	1.425 (1.149, 1.767)	**0.001****	1.371 (1.103, 1.704)	**0.005****

Both univariable analyses and multivariable correction for age and disease duration at study inclusion, sex, ATA seropositivity, lcSSc *vs* dcSSc and modified Rodnan skin score were performed. After multivariable corrections, only T2 ratio and LGE remained significant predictors of ventricular and any type of rhythm disturbances. No variables significantly predicted supraventricular rhythm disturbances after multivariable corrections. All *P*-values were corrected for multiple comparisons with a Benjamini–Hochberg test (false discovery rate 0.05) before being considered for significance. *P-value ⩽ 0.05 but non-significant after correction for multiple comparisons. **P-value ⩽ 0.05 and significant after correction for multiple comparisons. Bold type indicates statistical significance. CMR: cardiovascular magnetic resonance; ATA: anti-topoisomerase I antibodies; LGE: late gadolinium enhancement % of left ventricular mass; OR: odds ratio; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; LVEF: left ventricular ejection fraction; LV mass: left ventricular mass; RVEDV: right ventricular end diastolic volume; RVESV: right ventricular end systolic volume; RVEF: right ventricular ejection fraction.

FIG. 1 The SAnCtUS scoring system
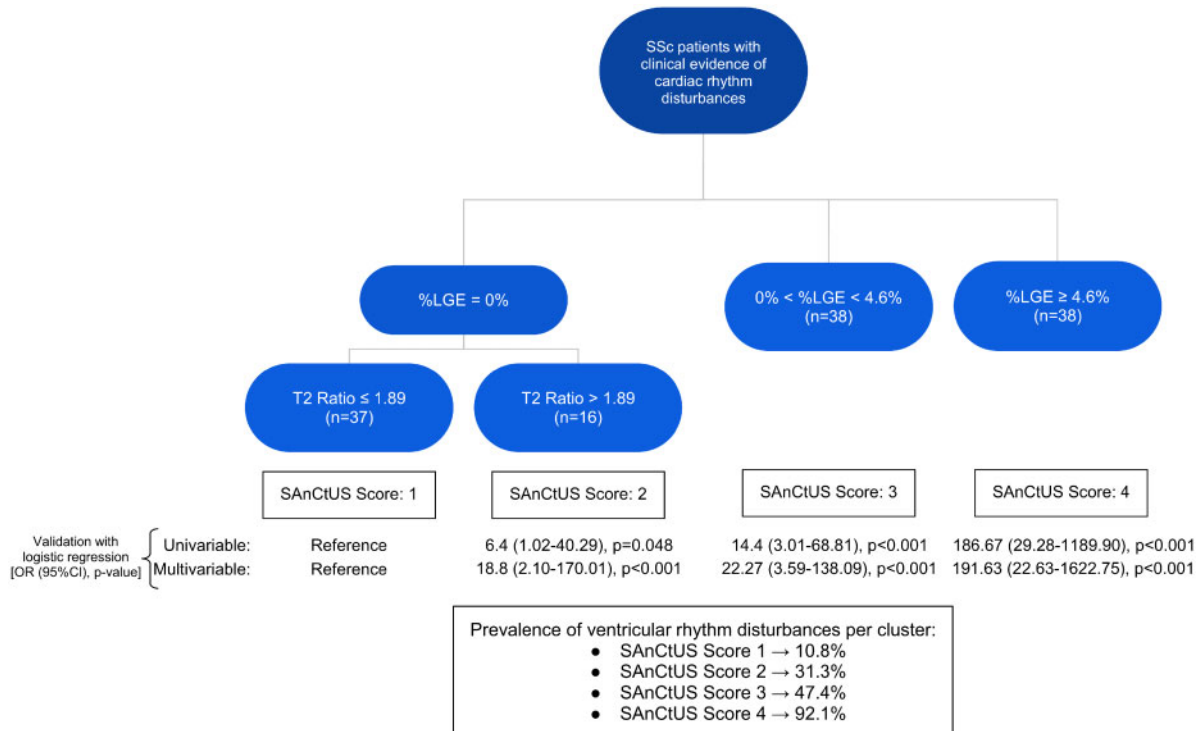
Ventricular rhythm disturbances were more prevalent with increasing scores ($P < 0.001$). LGE: late gadolinium enhancement; OR: odds ratio; SAnCtUS: Scleroderma Arrhythmia Clinical Utility Study; ATA: anti-topoisomerase I antibodies; LVEF: left ventricular ejection fraction.

Patients without detectable LGE were further subclassified based on their T2 ratio values. We calculated a cut-off of 1.89 for defining SAnCtUS score 1 (%LGE = 0%, T2 ratio $\leqslant 1.89$) and SAnCtUS score 2 (%LGE = 0%, T2 ratio >1.89). Subsequently, the algorithms defined the two remaining clusters exclusively based on %LGE values. We calculated a cut-off value of 4.6% for %LGE for defining SAnCtUS score 3 ($0\% < \%LGE < 4.6\%$) and SAnCtUS score 4 (%LGE $\geqslant 4.6\%$).

We subsequently validated the ability of the SAnCtUS score to predict ventricular rhythm disturbances with logistic regression analysis (Fig. 1). Increasing SAnCtUS scores predicted the occurrence of baseline ventricular rhythm disturbances in univariable analysis and remained significant after multivariable correction for the same confounders as in previous logistic models with the inclusion of LVEF. In univariable logistic regression, SAnCtUS score values achieved an area under the curve of 0.871, which increased to 0.907 after multivariable corrections. However, the univariable and multivariable model did not differ significantly based on the likelihood ratio test ($P = 0.073$).

Baseline characteristics were also compared between patients scored with each SAnCtUS score number (Table 1). In general, higher SAnCtUS scores were associated with greater arrhythmic burden and all cases of

non-sustained VT ($n = 7$) occurred in patients with a SAnCtUS score of 4 ($P < 0.001$). Median LVEF did not differ significantly between groups ($P = 0.096$). Higher SAnCtUS scores were significantly associated with a higher percentage of patients with LVEF $<55\%$ [from score 1 to 4: 1 (3%) vs 1 (6%) vs 4 (11%) vs 10 (26%), $P = 0.014$] and LVEF $<50\%$ [from score 1 to 4: 0 (0%) vs 0 (0%) vs 1 (3%) vs 6 (16%), $P = 0.014$]; however, the proportion of patients with LVEF $\leqslant 35\%$ did not differ significantly between groups ($P = 0.182$). Baseline characteristics are compared between patients with and without available SAnCtUS scores in supplementary Table S1, available at *Rheumatology* online.

Of the 145 (96.7%) patients with available 1-year clinical follow-up (total time at risk: 40 736 days), 14 (9.7%) experienced the combined endpoint. One patient was excluded because the cause of death was deemed non-cardiovascular, and another because the SAnCtUS score could not be calculated. Of the remaining 12 patients, 10 (6.2%) were hospitalized due to episodes of sustained VT, and all were successfully treated with ICD implantation. SCD occurred in an additional two (13.8%) patients. With the exception of a single patient (8.3%), all patients that were hospitalized or died due to cardiac-related causes had no documented evidence of VT in their baseline 24 h Holter recordings. However, almost all had a SAnCtUS

score of 3/4 (scores 1/2 *vs* 3/4: 1 *vs* 11, *P* = 0.017). Specifically, one (8.3%) patient had a score of 2, four (33.3%) had a score of 3 and seven (58.3%) had a score of 4. Only 3 of 12 (25%) patients that reached the combined endpoint had an LVEF <55% and only 2 of 12 (16.7%) had an LVEF <50% at baseline CMR scans, while no patient had an LVEF ≤35%. In multivariable Cox regression analysis, having a SAnCtUS score of 3/4 conveyed a hazard ratio of 7.96 (95% CI: 1.01, 62.61, *P* = 0.048) for the combined endpoint compared with scores 1/2, independently of age, sex, disease duration and New York Heart Association functional class. Similarly, having a SAnCtUS score of 4 conveyed a hazard ratio of 3.86 (95% CI: 1.14, 13.04, *P* = 0.029) compared with scores 1/2/3 when corrected for the same confounders. In contrast, LVEF and baseline findings of VT in 24 h Holter were not significant in comparable analyses [0.96 (95% CI: 0.91, 1.02), *P* = 0.154; and 1.38 (95% CI: 0.17, 10.10), *P* = 0.760, respectively].

Discussion

In the SAnCtUS cohort 48.7% of patients experienced one or more types of clinically relevant rhythm disturbances at baseline. Using decision-tree analysis, we generated and calibrated the SAnCtUS score, a four-category scoring system based on T2 ratio and %LGE, for identifying SSc patients at high risk of experiencing ventricular rhythm disturbances. This was independent of laboratory, history or clinical covariates including LVEF. Increasing SAnCtUS scores were associated with a greater prevalence of most types of rhythm disturbances at baseline, the dcSSc subset and anti-topoisomerase I antibody positivity. All cases of non-sustained VT (*n* = 7) at baseline occurred in patients scored with the highest SAnCtUS score value (=4). Clinical follow-up at one year after study inclusion, available for 145 (96.7%) patients, showed that those who experienced adverse outcomes were classified in the highest SAnCtUS score categories (3 or 4) and their identification by the presence of baseline VT or pathologic LVEF was suboptimal. Cox regression analyses further confirmed these findings.

A recent histopathologic study on 25 SSc patients reported an association between cardiac event rates and the severity of myocardial inflammation and fibrosis, with only mild LVEF impairments, which is in complete agreement with our findings [25]. Furthermore, only 16% of patients scored in the highest risk category based on the SAnCtUS score had an LVEF <50% and no patient had an LVEF ≤35%. Systolic and diastolic left and right ventricular volumes were all significant univariable predictors of any type and supraventricular rhythm disturbances. However, they offered little additional value when corrected for laboratory, history and clinical parameters. Current evidence suggests that myocardial inflammation and fibrosis is common in SSc and that fibrosis might be due to vascular spasm, with otherwise normal coronary arteries [14, 29, 30]. The association between inflammation or fibrosis and rhythm disturbances documented in SAnCtUS is thus highly significant as SSc patients are

usually assessed with echocardiography based on ventricular function. In contrast, CMR is the only non-invasive imaging modality that can simultaneously provide tissue characterization and functional information for both ventricles. Most importantly, even within CMR-derived indices, we demonstrate that measures of myocardial oedema and replacement fibrosis performed better than ventricular volumes, ejection fractions and left ventricular mass when identifying patients at risk for cardiac rhythm disturbances, independently of known confounding factors.

As stated previously, the Scleroderma Clinical Trial Consortium emphasized that rhythm disturbances in SSc patients negatively affect prognosis [9]. Therefore, early detection of high-risk patients is of paramount importance. However, the study of the Scleroderma Clinical Trial Consortium gave less emphasis to CMR [9], only citing a small single-centre study demonstrating that SSc patients with normal 24 h Holter recordings had a lesser extent of fibrosis than those with abnormal 24 h Holter [31]. The study did not have long-term follow-up and confounding factors were not taken into account. A more recent study suggesting that LGE is not a good predictor of arrhythmic burden is SSc suffered from similar limitations [32]. Another study proposed a threshold of PVC >1190/h for predicting adverse outcomes in SSc, yet this is methodologically questionable as this was not derived from a time-dependent receiver operating characteristic curve analysis and multivariable analyses were not performed. Additionally, imaging evaluation was limited to echocardiography [33]. Another study evaluated SSc patients with myocarditis, the majority of whom had pathologic CMR findings [34]. However, CMR was performed in only seven patients. To our knowledge, our study is the first multicentre study to incorporate cardiac rhythm disturbances, CMR indices, laboratory, history and clinical parameters, and with 1-year follow-up in a sufficiently large and varied population of consecutive SSc patients.

An important innovation of our study was the creation of the SAnCtUS scoring system. Firstly, identification of inflammation by CMR may guide treatment [35]. Secondly, in our study patients with high SAnCtUS scores were at significantly higher risk of SCD often without pathologic LVEF values or previous evidence of VT on baseline 24 h Holter, and as such the SAnCtUS score may act as a complementary indication for ICD implantation. Thirdly, a new role for CMR in SSc is emerging, as autologous haematopoietic stem cell transplantation conveys long-term event-free survival benefits in dcSSc patients. Despite these advantages, the high mortality in the autologous haematopoietic stem cell transplantation group was in part attributed to VT or ventricular fibrillation [36]. Therefore, patients eligible for autologous haematopoietic stem cell transplantation should be examined with CMR for risk stratification.

Use of biomarkers for patient pre-selection for CMR evaluation may be considered. We have previously demonstrated that CMR findings appear to be independent of CRP, ESR, N-terminal pro-brain-type-natriuretic

peptide or cardiac troponin-T in autoimmune rheumatic diseases [37]. Current evidence suggests that N-terminal pro-brain-type-natriuretic peptide and cardiac troponin-I levels might indicate right cardiac stress, mainly in association with pulmonary hypertension [38, 39]. Nevertheless, N-terminal pro-brain-type-natriuretic peptide is dependent on numerous factors (obesity, sex/age, renal function) [40] and cardiac troponin-T/cardiac troponin-I is organ- but not disease-specific [41]. Because these indices were not investigated in this study, further research is required to identify the exact niche where these can potentially be used in the context of diagnostic guidelines for primary heart involvement in SSc.

Limitations

T1/T2-mapping and extracellular volume fraction offer incremental value beyond traditional CMR indices and can guide ICD implantation in autoimmune rheumatic disease patients with VT and preserved LVEF [42]. Despite not being evaluated in this study, they are dependent on hardware, acquisition methods and standardization with healthy controls, which may lead to between-centre differences. Additionally, no endomyocardial biopsies or electrophysiologic data were available and thus further studies are needed before the proposed scoring system is extrapolated to clinical practice. Furthermore, the small number of ACA-seropositive patients and the lack of sufficient long-term follow-up limited our ability to identify associations between SAnCtUS scores and antibody titres or long-term outcomes. Lastly, to ensure external validity, it should be noted that left ventricular end diastolic volume was identified as a variable of interest in random forest analysis, and despite not being a significant identifier in this cohort it should be re-evaluated in future studies.

Conclusions

Among CMR indices, T2 ratio and %LGE had the greatest utility in predicting baseline and future life-threatening ventricular rhythm disturbances in SSc patients, independently of known disease covariates and LVEF. The SAnCtUS score based on T2 ratio/%LGE allowed for stratification of SSc patients at risk for future SCD and was superior to both baseline LVEF and baseline VT occurrence. We demonstrate that the underutilized baseline 24 h Holter findings can be substantiated by CMR into a tangible risk prediction score, which outperforms currently used methods and might eventually constitute an indication for ICD implantation in SSc patients if future studies further validate and support these findings.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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