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Title Abnormal electrophysiological testing associates with future incidental significant arrhythmia in Scleroderma

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Sir, sudden death from scleroderma heart disease-associated arrhythmia is a well-recognised cause of mortality in systemic sclerosis (SSc) [1]. There is no systematic approach to screening in SSc, with an electrocardiogram (ECG) and 24 hour ambulatory ECG (24h ECG) usually requested on clinical indication. These methods cover a short period of time and may often only demonstrate non-specific, typically benign findings [2, 3]. We recently reported the detection of incidental significant arrhythmias in a cohort of patients with SSc using an implantable loop recorder (ILR) [4]. We now report on a secondary analysis to explore if baseline short-term electrophysiological (EP) changes differed in those who developed significant arrhythmias over the study period.

As previously reported, 19 patients with SSc (free of cardiovascular disease, diabetes and no more than one traditional cardiovascular risk factor) were consented into the ELCASA (ELectrophysiology and CArdiac imaging in SclerodermA) study. Patient evaluation included signal averaged ECG (SAE), 24h ECG and autonomic testing, serum cardiac biomarker measurement (creatine kinase (CK), high-sensitivity troponin I (Hs-TnI), N-terminal pro brain natriuretic peptide (NT-proBNP)), contrast-enhanced 3T cardiac magnetic resonance imaging (CMR), followed by ILR insertion, and three-monthly review for three years [4]. SAE detects the presence of late ventricular potentials, which can indicate myocardium at risk of arrhythmia and has been associated with cardiac fibrosis in SSc [5]. The supplementary file details definition of abnormal SAE and autonomic testing. Abnormal 24h ECG was defined as the presence of supraventricular tachycardia, atrial fibrillation, flutter, ventricular tachycardia, couplets, triplets, dropped beats, pauses or bradycardia.

Of the 19 patients, 63% were female, mean (SD) age of 53 (12) years, and 32% had diffuse SSc (dcSSc). Over three years, eight developed significant arrhythmias; 1 complete heart

block (CHB), 2 non-sustained ventricular tachycardia (NSVT) and 5 atrial arrhythmias [4]. Only one patient was symptomatic with palpitations at the time of the arrhythmia (NSVT).

Of the data available, patients who developed arrhythmias over three years were more likely to have at baseline an abnormal SAE (3/4 (75%) vs. 1/9 (11%) with no arrhythmia), autonomic testing (3/5 (60%) vs. 3/9 (33%)) and 24h ECG (5/6 (83%) vs. 3/10 (30%)) (see Table 1 and S1). Six patients (3 male, 4 dcSSc, 3 history of ILD, 2 history of DU) had 2 or more abnormal EP tests and 4 went on to develop an arrhythmia. All three EP tests were abnormal in two patients, both developing subsequent arrhythmia (1 male, both dcSSc, 1 history of ILD, 1 history of DU).

Patients with abnormal EP tests at baseline tended to have notably higher cardiac serum biomarkers. The mean differences (95% CI) in NT-proBNP for those with abnormal SAE, autonomic testing and 24h ECG were 44 (-154, 241)ng/l, 125 (-53, 303) and 164 (47, 281)ng/l respectively). A similar result was seen with Hs-TnI and CK (see Table S2).

Except for a trend for reduced LV mass and myocardial perfusion reserve in those with abnormal baseline EP tests, no other CMR indices appeared to be associated (see Table S2). Only 1 of 4 patients with late gadolinium enhancement (LGE) focal fibrosis had abnormal baseline EP testing.

These data reveal that those developing significant arrhythmias over three years were more likely to have (multiple) abnormal EP tests at baseline; with abnormal findings associated with higher serum cardiac biomarkers. This is consistent with our published primary analysis where ILR-detected significant arrhythmia were associated with higher baseline cardiac biomarkers [4].

Although a pilot study with a small number of patients and not powered to show statistical differences, these findings suggest a composite of non-invasive EP investigations, serum cardiac biomarkers, and CMR could inform the use of ILR to pre-empt scleroderma heart disease-associated arrhythmias and reduce associated mortality.

Table 1: Baseline electrophysiological results in study patients, comparing those developing and not developing significant arrhythmias over the three years.

	All patients (n=19)	**Patients developing arrhythmias (n=8)**	**Patients not developing arrhythmias (n=11)**
Abnormal signal averaged ECG	4/13 (21)	3/4 (75)	1/9 (11)
Abnormal autonomic testing	6/14 (43)	3/5 (60)	3/9 (33)
Abnormal 24 hour ambulatory ECG	8/16 (50)	5/6 (83)	3/10 (30)
2 or more of above EP tests abnormal	6/15 (40)	4/5 (80)	2/10 (20)
All 3 above EP tests abnormal	2/12 (17)	2/4 (50)	0/8 (0)

Values expressed as n (%)
ECG, electrocardiogram; EP, electrophysiological

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