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Electrocardiographic detection of pulmonary hypertension in patients with systemic sclerosis using the ventricular gradient☆

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Abstract

Background: Pulmonary hypertension (PH) is a leading cause of death in systemic sclerosis (SSc) patients. The current study assessed the ability of the ECG-derived ventricular gradient (VG-RVPO) to detect PH and predict all-cause mortality in PH patients with subtypes of SSc differing in the extent of multi-organ involvement.

Methods: ECGs were obtained from 196 patients with limited and 77 patients with diffuse SSc included from our screening programme on cardiac complications. The association of the VG-RVPO with (1) the presence of PH, (2) conventional screening parameters and (3) survival in PH patients was assessed.

Results: In limited SSc patients an elevated VG-RVPO corresponded with the presence of PH (-5 ± 12 mV.ms vs -22 ± 16 mV.ms, $P < 0.01$), correlated significantly with conventional screening parameters and had a better diagnostic performance than the presence of a right heart axis (AUC 0.81 vs 0.60; $P = 0.04$). These differences were not observed in patients with diffuse SSc. An elevated VG-RVPO was associated with decreased survival in all SSc patients with PH (3 year survival 30% vs 64%, $P = 0.02$).

Conclusion: An elevated VG-RVPO is associated with PH in limited SSc patients and with decreased survival in all SSc patients with PH.

Keywords: Electrocardiogram; Ventricular gradient; Pulmonary hypertension; Right ventricular pressure overload; Systemic sclerosis

Introduction

Pulmonary hypertension (PH) is a leading cause of death in systemic sclerosis (SSc). SSc is an auto-immune connective tissue disorder characterised by small vessel disease, production of auto-antibodies and fibroblast dysfunction. SSc is expressed in phenotypes that differ in the amount and location of skin and organ involvement. This variation in phenotypes is reflected in the so-called clinical subtypes limited and diffuse SSc [1,2]. At immunologic level these subtypes differ in expression of antibodies. Patients with limited SSc more often exhibit anticentromere antibodies (ACA), whereas patients with diffuse SSc express anti-topoisomerase I antibodies (anti-Scl-70) more frequently. Typically, patients with limited SSc are prone to the development of pulmonary arterial hypertension (PAH), whilst patients with diffuse SSc are at greater risk for development of interstitial lung disease, oliguric renal failure and myocardial involvement [2–5].

Different etiologies of pulmonary pressure elevation are observed in patients with SSc. PAH relates to obstructive proliferative vasculopathy and is categorised as group I according to the World Health Organisation (WHO) classification for PH [6]. PAH develops in about 5–14% of SSc patients and 1-year mortality rates up to 30% are reported, which is twice as high as in idiopathic PAH [2–4,7,8]. Left ventricular heart disease and advanced interstitial lung disease are other possible clinical features of SSc and can result in respectively PH group II and III [2,4,9]. Especially in SSc patients PH can progress rapidly, resulting in right ventricular (RV) pressure overload and eventually right sided heart failure with significant decreased survival [3,4]. Early diagnosis and treatment of PH may

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improve quality of life and outcome in these patients [3]. However, initial symptoms of the disease are frequently non-specific, which can result in delay between onset of symptoms and diagnosis [4]. This emphasises the need for adequate screening tools to detect patients with asymptomatic or mildly symptomatic disease, in order to improve outcome through early treatment. For this purpose, the most frequently used non-invasive screening tool is echocardiography [3,4]. However, the electrocardiogram (ECG) might play an important additional role because it is easier and faster to obtain at lower cost to compared echocardiography. Furthermore, the ECG is an important alternative when echocardiography is inconclusive due to insufficient image quality or absent tricuspid regurgitation.

In PH the ECG changes as a result of structural and functional RV adaptations. Most importantly, heart rate increases and the magnitude and direction of ventricular de- and repolarisation forces change due to increased RV wall stress and hypertrophy [10–12]. Previous studies demonstrated that the electrocardiographically derived ventricular gradient (VG) can accurately detect increased pulmonary pressures when projected in the optimal direction for detection of RV pressure overload (VG-RVPO) in a heterogeneous population suspected of PH [10,12,13]. However, the value of the VG-RVPO is still unknown in patients with SSc, who are at increased risk for development of PH. Moreover, previous research has shown VG alterations in other forms of cardiac disease [14]. Therefore it is of particular interest to investigate whether myocardial involvement, as more frequently seen in patients with the diffuse subtype, leads to changes in the VG-RVPO not related to pulmonary pressure elevation, thus altering the clinical applicability. Therefore the aim of the current study was firstly to assess the association between the VG-RVPO and PH in patients with SSc subdivided in clinical subtypes. The second aim was to analyse the association between the VG-RVPO and conventional screening parameters for PH in this patient population. Thirdly the association between the VG-RVPO and all-cause mortality in PH patients was assessed. It was hypothesised that a low VG-RVPO identifies patients at low risk of PH and that the diagnostic accuracy of the VG-RVPO is likely to be lower in patients with diffuse SSc.

Methods

Patient population

The study population comprised patients with SSc who were referred to the cardiology out-patient clinic for routine screening on cardiac complications including PH between January 2009 and January 2014. History, physical examination, blood sampling, ECG, echocardiography and pulmonary function test were routinely obtained as part of the care programme. All patients were treated according to current recommendations [15]. Baseline characteristics, SSc specific features, functional class, 6-minute walking distance and clinical presence of left sided heart disease were prospectively collected from our electronical patient data system and retrospectively analysed. In patients with PH the data prior to diagnosis of PH were used for analysis. Patients with pacemaker rhythm or not interpretable ECGs were excluded from analysis. All-cause mortality was registered during follow-up through case record review and the national death registry. The study was conducted in accordance with the declaration of Helsinki and approved by the Leiden University Medical Center Institutional Review Board.

SSc classification

Since the study aimed to assess potential differences in VG-RVPO between clinical subtypes, patients were classified as having diffuse or limited SSc according to the LeRoy criteria [16]. However, a drawback of the LeRoy criteria is that patients with early and limited cutaneous disease frequently do not meet the classification criteria for SSc. To increase sensitivity for detection of patients with early and limited SSc, Van den Hoogen et al. have recently proposed a new classification algorithm that does not distinguish between SSc subtypes [1]. For the purpose of the current analysis it was verified that subdivision in limited and diffuse SSc indeed resulted into distinct patient groups. Table 1 demonstrates differences in expression of ACA and anti-Scl-70 and presence of interstitial lung disease and left sided heart disease between both subtypes.

Laboratory test

Routine laboratory testing included measurement of N-terminal pro-brain natriuretic peptide (pro-BNP) level in ng/L (normal value 0–200 ng/L, electrochemiluminescence immunoassay, Roche Diagnostics).

Pulmonary function test

Pulmonary function tests included spirometry and gas transfer studies. Total lung capacity (TLC) was measured through the multiple breath helium dilution method and diffusion capacity for carbon monoxide (DLCO) was measured through the single breath carbon monoxide method [17,18]. All values are expressed as percentage of the normalised value according to age, gender, height, weight and race.

Electrocardiography

Heart rate, QRS duration, QTc duration and heart axis were retrieved from conventional ECG recordings. Furthermore the VG-RVPO was computed using our dedicated software programme LEADS [19]. This programme analyses

Table 1
Differentiation between limited and diffuse SSc.

	Limited SSc n = 196	Diffuse SSc n = 77	P
ACA (%)	52	6	<0.01
Anti-Scl-7 (%)	47	68	<0.01
Interstitial lung disease (%)	47	69	<0.01
Left sided heart disease (%)	2	4	0.23

SSc, systemic sclerosis; ACA, anticentromere antibody; anti-Scl-70, anti-topoisomerase I antibody.