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Part III

Right Ventricular Overload in Diseases Associated with Pulmonary Arterial Hypertension
Chapter 7

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 (area under the curve 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).

**Conclusions**

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 autoimmune connective tissue disorder characterized 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 anticientromere 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), while 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 categorized as group I according to the World Health Organization (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.\(^1,4\) Early diagnosis and treatment of PH may 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 emphasizes 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 compared to 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 result of structural and functional RV adaptations. Most importantly, heart rate increases and the magnitude and direction of ventricular de- and repolarization 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.\textsuperscript{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.\textsuperscript{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 hypothesized 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.

\textit{Methods}

\textbf{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.\textsuperscript{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.

\textbf{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.\textsuperscript{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 and colleagues have recently proposed a new classification
algorithm that does not distinguish between SSc subtypes. 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.

Table 1. Differentiation between limited and diffuse SSc.

<table>
<thead>
<tr>
<th></th>
<th>Limited SSc</th>
<th>Diffuse SSc</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACA (%)</td>
<td>52</td>
<td>6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anti-Scl-7 (%)</td>
<td>47</td>
<td>68</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Interstitial lung disease (%)</td>
<td>47</td>
<td>69</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left sided heart disease (%)</td>
<td>2</td>
<td>4</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Abbreviations: SSc, systemic sclerosis; ACA, anticientromere antibody; anti-Scl-7; anti-topoisomerase I antibody.

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. All values are expressed as percentage of the normalized 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 program LEADS. This program analyses standard 10-second 12-lead ECGs and semi-automatically performs vectorcardiographic calculations on the electrical signal of the averaged heartbeat. The VG is a vectorial measure and thus has a magnitude and spatial orientation. It comprises the area under the QRS-T complex in 3 dimensions and therefore represents the net electrical activity during de- and repolarization. Pathological changes in myocardial properties result in VG alterations. Figure 1 depicts the changes in VG from the normal cardiac situation to respectively early and end-stage PH.
As demonstrated previously, the magnitude of the VG can be calculated in a prespecified projection (elevation 27° and azimuth 155°), thereby accentuating the contribution of the right ventricle to the VG vector. This projection is optimized for detection of RV overload and therefore referred to as VG-RVPO.

Figure 1. Change in cardiac vectors from the normal physiologic situation to respectively early stage and chronic PH.

Echocardiography

Transthoracic echocardiographic images were obtained in left lateral decubitus and supine position with a commercially available system (Vivid 7 or E9 [General Electric-Vingmed ultrasound, Horten, Norway]) and digitally stored in cine-loop format. Analysis was performed using commercially available software (EchoPAC version 112.0.1; General Electric-Vingmed ultrasound, Horten, Norway). Standard 2-dimensional images were obtained. The maximum tricuspid regurgitant jet (TR) gradient was measured on the 4-chamber view using the modified Bernoulli equation. Right atrial pressure was estimated as 3, 8, 13 or 18 mmHg based on the diameter and inspiratory collapse of the inferior caval vein. Systolic pulmonary arterial pressure (SPAP) was calculated by summation of tricuspid regurgitant gradient and right atrial pressure. An elevated sPAP was defined as a pressure ≥36 mmHg.

PH classification

PH was categorized according to the WHO classification for PH. Patients with an elevated SPAP on echocardiography were individually evaluated in a multidisciplinary team with regard to underlying etiology, clinical functioning and right heart hemodynamics. According to international guidelines, right heart catheterization for invasive assessment of pulmonary hemodynamics was only performed in patients suspected of PAH (WHO group I). PAH was defined as mean pulmonary arterial
pressure (MPAP) ≥25 mmHg, pulmonary arterial wedge pressure ≤15 mmHg and pulmonary vascular resistance ≥3 Wood Units.23 PH in the presence of left sided heart disease or severe pulmonary disease was diagnosed based on history, pulmonary function test and signs of elevated pulmonary pressures and RV overload on echocardiography.

**Statistical analysis**

SPSS for Windows (version 20.0, Chicago, Illinois) was used for statistical analysis. Continuous variables are expressed as mean ± standard deviation when normally distributed, or otherwise as median and interquartile range (IQR). Differences in continuous variables were assessed using the Student-t test or non-parametric test when not normally distributed. Categorical data are presented as frequencies and percentages and differences were assessed using the Chi-square test. Bar charts and receiver operating characteristic (ROC) curves were computed to compare the VG-RVPO with screening parameters conventionally used to detect patients at high risk for PH. Differences in VG-RVPO between patients with a normal and right heart axis and between patients with a normal and elevated SPAP were assessed using the Student-t-test. Linear regression analysis was used to assess the association between the VG-RPO and different pro-BNP categories. Diagnostic accuracy of both the VG-RVPO and the presence of a right heart axis was assessed by comparing the areas under the curve (AUC) according to the method proposed by Hanley and McNeil24. Furthermore, diagnostic accuracy was computed for different VG-RVPO cut-offs that were selected with regard to clinical relevancy on the basis of the first analyses. Next, cumulative survival rates were calculated according to the Kaplan Meier method for patients with PH divided in normal and elevated VG-RVPO and a log rank test was performed to assess differences between these curves. Hazard ratios (HR) and 95% confidence intervals (95% CI) for mortality in the elevated versus the normal VG-RVPO category were calculated using Cox regression analysis. P-values <0.05 were considered statistically significant.

**Results**

**General and disease specific characteristics of the patient population**

Figure 2 provides a clinical flow chart of the patient population. PH was diagnosed in 13 out of 196 patients (age 67.9±10.3 years, 15% males) with limited SSc and in 7 out of 77 patients (age 61.7±15.1 years, 14% males) with diffuse disease and was classified according to the WHO classification for PH.
Table 2 summarizes clinical characteristics of the population, categorized based on SSc subtype and the presence of PH. Patients diagnosed with PH tended to be older in both the limited and diffuse SSc group. Furthermore, all patients with PH had significant worse functional class, higher pro-BNP levels and shorter 6-minute walking distances as compared to patients without PH. DLCO measured during pulmonary function test was lower in patients with PH. Next, heart rate was significantly higher in PH patients. In the limited SSc group, a right heart axis was more frequently present in patients with PH than in patients without PH. In diffuse SSc however this difference did not reach statistical significance. Moreover, the VG-RVPO was significantly higher in PH patients compared to patients without PH (-5 ± 12 mV.ms vs -22 ± 16 mV.ms, P<0.01) in patients with the limited SSc subtype. No significant relation was found between the VG-RVPO and PH in patients with diffuse SSc.
### Table 2. Clinical characteristics of the population.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Limited SSc</th>
<th></th>
<th>Diffuse SSc</th>
<th></th>
<th>P</th>
<th></th>
<th>PH</th>
<th>No PH</th>
<th>P</th>
<th>PH</th>
<th>No PH</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.9±10.3</td>
<td>56.9±14.0</td>
<td>&lt;0.01</td>
<td>61.7±15.1</td>
<td>53.9±13.6</td>
<td>0.16</td>
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<td></td>
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<tr>
<td>Sex (% males)</td>
<td>15</td>
<td>14</td>
<td>0.86</td>
<td>14</td>
<td>24</td>
<td>0.55</td>
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<tr>
<td>Duration SSc (years)</td>
<td>1 (IQR 0 – 6.5)</td>
<td>2 (IQR 0 – 10)</td>
<td>0.17</td>
<td>8 (IQR 5 – 17)</td>
<td>5 (IQR 2 – 10)</td>
<td>0.20</td>
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<td>Interstitial lung disease (%)</td>
<td>50</td>
<td>47</td>
<td>0.88</td>
<td>75</td>
<td>69</td>
<td>0.79</td>
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<tr>
<td>Left sided heart disease (%)</td>
<td>8</td>
<td>1</td>
<td>0.06</td>
<td>14</td>
<td>3</td>
<td>0.14</td>
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<tr>
<td>Functional class I/II/III/IV (%)</td>
<td>0/82/0/18</td>
<td>83/17/0/0</td>
<td>&lt;0.01</td>
<td>40/20/20/20</td>
<td>65/30/5/0</td>
<td>&lt;0.01</td>
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<td>6-minute walk distance (m)</td>
<td>265±104</td>
<td>518±127</td>
<td>&lt;0.01</td>
<td>234±80</td>
<td>510±126</td>
<td>&lt;0.01</td>
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<td>Pro-BNP level (ng/l)</td>
<td>1445±1309</td>
<td>199±345</td>
<td>0.03</td>
<td>2785±2430</td>
<td>230±404</td>
<td>0.08</td>
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<td>Echocardiography</td>
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<td>TR gradient (mmHg)</td>
<td>54±11</td>
<td>23±5</td>
<td>&lt;0.01</td>
<td>50±22</td>
<td>23±6</td>
<td>0.02</td>
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<td>Estimated SPAP (mmHg)</td>
<td>63±14</td>
<td>27±6</td>
<td>&lt;0.01</td>
<td>52±23</td>
<td>27±6</td>
<td>&lt;0.05</td>
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<td>Pulmonary function test</td>
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<td>TLC (% predicted)</td>
<td>74±20</td>
<td>91±15</td>
<td>&lt;0.01</td>
<td>60±18</td>
<td>82±18</td>
<td>0.02</td>
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<tr>
<td>DLCO (% predicted)</td>
<td>37±9</td>
<td>67±16</td>
<td>&lt;0.01</td>
<td>29±14</td>
<td>61±16</td>
<td>&lt;0.01</td>
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<td>ECG</td>
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<tr>
<td>Heart rate (bpm)</td>
<td>84±15</td>
<td>69±12</td>
<td>&lt;0.01</td>
<td>89±16</td>
<td>70±12</td>
<td>&lt;0.01</td>
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<tr>
<td>QRS duration (ms)</td>
<td>99±13</td>
<td>95±15</td>
<td>0.29</td>
<td>109±41</td>
<td>101±18</td>
<td>0.63</td>
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<tr>
<td>QTc duration (ms)</td>
<td>417±32</td>
<td>409±21</td>
<td>0.39</td>
<td>425±39</td>
<td>405±23</td>
<td>0.04</td>
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<tr>
<td>Right heart axis (%)</td>
<td>23</td>
<td>3</td>
<td>&lt;0.01</td>
<td>14</td>
<td>4</td>
<td>0.26</td>
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<tr>
<td>VG-RVPO (mV.ms)</td>
<td>-5±12</td>
<td>-22±16</td>
<td>&lt;0.01</td>
<td>-14±19</td>
<td>-23±17</td>
<td>0.17</td>
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</table>

Abbreviations: SSc, systemic sclerosis; PH, pulmonary hypertension; pro-BNP, N-terminal pro-Brain Natriuretic Peptide; TR, maximum tricuspid regurgitant jet; SPAP, systolic pulmonary arterial pressure; TLC, total lung capacity; DLCO, diffusion capacity for carbon monoxide; VG-RVPO, ventricular gradient - right ventricular pressure overload.

The VG-RVPO compared to conventional PH screening parameters

Relations between the earlier described conventional PH screening parameters and the VG-RVPO are graphically demonstrated in Figure 3. A higher pro-BNP level, the presence of a right heart axis and an elevated SPAP all correlated significantly with a higher VG-RVPO in patients with limited SSc. This difference was not observed in patients with diffuse SSc.
Figure 3. Conventional screening parameters of pulmonary hypertension compared to the VG-RVPO in limited and diffuse SSc. Bar charts of the VG-RVPO in patients with limited and diffuse SSc plotted against pro-BNP levels categorized in <200, 200-500, 500-1000 and >1000 (A), the presence of a right heart axis (B) and an elevated SPAP (≥36 mmHg) on TTE (C).

Abbreviations: VG-RVPO, ventricular gradient - right ventricular pressure overload; SSc, systemic sclerosis; pro-BNP, N-terminal pro-Brain Natriuretic Peptide; SPAP, systolic pulmonary arterial pressure.

Furthermore, only in patients with limited SSc the VG-RVPO had a significantly better diagnostic performance for detection of PH than the right heart axis (Figure 4). Comparison of ROC curves revealed an AUC of 0.81 for the VG-RVPO versus an AUC of 0.60 for the presence of a right heart axis (P=0.04). In patients with diffuse SSc the contribution of both the VG-RVPO and the presence of a right heart axis in diagnosing PH appeared limited (AUC 0.61 vs 0.55, P=0.62). Moreover, heart axis as a continuous variable did not provide additional diagnostic information in limited nor diffuse SSc (AUC respectively 0.49 and 0.54).
Ventricular gradient in Systemic Sclerosis and Pulmonary Hypertension

Figure 4. ROC curves for the VG-RVPO compared to the presence of a right heart axis in limited SSc (A) and diffuse SSc (B).

Abbreviations: VG-RVPO, ventricular gradient - right ventricular pressure overload; SSc, systemic sclerosis.

Diagnostic accuracy and mortality assessment

Diagnostic accuracy for the detection of PH was calculated for different VG-RVPO cut-offs (Table 3). A cut-off value of -7 mV.ms performed best in identifying patients at low risk for PH with a specificity of 86% and a negative predicting value of 97%. During follow-up 9 out of 13 patients with limited SSc and PH and 3 out of 7 patients with diffuse SSc and PH died. Figure 5 depicts the survival characteristics of patients with PH subdivided in 2 groups according to the VG-RVPO (black line: ≤-7 mV.ms; dotted line >-7 mV.ms). A higher VG-RVPO correlated with increased mortality in SSc patients with PH (HR 4.49, 95% CI 1.15-17.53, P=0.03). Survival 3 years after ECG recording was 49% in the total population with PH; 64% in the group with a VG-RVPO ≤-7 mV.ms compared to 30% in the group with a VG-RVPO >-7 mV.ms.

Table 3. Diagnostic accuracy of different VG-RVPO cut-offs.

<table>
<thead>
<tr>
<th>VG-RVPO cut-off</th>
<th>Limited SSc</th>
<th>Diffuse SSc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sens (%)</td>
<td>Spec (%)</td>
</tr>
<tr>
<td>&gt; -3 mV.ms</td>
<td>46</td>
<td>89</td>
</tr>
<tr>
<td>&gt; -5 mV.ms</td>
<td>54</td>
<td>86</td>
</tr>
<tr>
<td>&gt; -7 mV.ms</td>
<td>62</td>
<td>86</td>
</tr>
<tr>
<td>&gt; -9 mV.ms</td>
<td>69</td>
<td>81</td>
</tr>
</tbody>
</table>

Abbreviations: VG-RVPO, ventricular gradient - right ventricular pressure overload; SSc, systemic sclerosis; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value.
Figure 5. Kaplan Meier survival curves stratified by VG-RVPO ≤-7 and >-7 in SSc patients with pulmonary hypertension.

Abbreviations: VG-RVPO, ventricular gradient - right ventricular pressure overload; SSc, systemic sclerosis.

Discussion

Main findings of this study were: 1/ the VG-RVPO was significantly elevated in patients with PH and limited SSc compared to patients without PH, 2/ the VG-RVPO correlated well with conventional PH screening parameters and had a better diagnostic performance than the presence of a right heart axis in this group and 3/ an elevated VG-RVPO was associated with decreased survival in SSc patients with PH.

PH is a frequent complication in SSc resulting in elevated RV pressure, increased RV wall stress and RV remodelling with important consequences for treatment and prognosis. As soon as systolic RV pressure increases, initial changes occur on the ECG mainly in the repolarization phase, in general before RV hypertrophy becomes apparent. It was demonstrated in animal as well as in human studies that the ECG-derived VG is a sensitive marker for these subtle repolarization changes in response to RV pressure overload. Recent studies showed that the VG has a strong association with pulmonary pressure in a heterogeneous population of suspected PH patients. However, it remained to be determined whether these results could be extrapolated to SSc patients. Initially, Scherptong and colleagues used the projection of the VG on the X-axis. However, a limited number of SSc patients was included in this study and results were not reported separately for this population. Moreover, later studies demonstrated that optimal detection of RV overload is achieved when the VG is projected on a projection direction with an elevation of 27° and azimuth of 155°.

In the current study the latter VG projection was used, which demonstrated to be significantly higher in patients with limited SSc and PH compared to patients with limited SSc without PH. This difference
was not found in patients with diffuse SSc. A possible explanation for this finding could be that patients with diffuse SSc more frequently exhibit pulmonary and cardiac involvement which could result in obscuring of the electrical signal by electrophysiological changes not specifically related to pulmonary pressure elevation. Nonetheless, as previous studies show that especially patients with limited SSc are at greater risk of developing PH, the VG-RVPO has potential as screening marker in this specific patient population.\textsuperscript{5,7,27}

Previous studies already demonstrated altered ECG morphology in SSc patients compared to healthy controls, namely a larger number of premature supraventricular and ventricular contractions, less heart rate variability and a higher percentage of QTc prolongation in SSc patients.\textsuperscript{28,29} To our knowledge, few data are published concerning ECG differences between SSc clinical subtypes. Nordin and colleagues assessed conduction abnormalities, septal Q-wave patterns, ST-T wave abnormalities, QTc duration, premature contractions and heart rate variability between SSc subsets and found no significant differences, although this was a small study with 110 patients of which only 22\% was diagnosed with diffuse SSc.\textsuperscript{30} In the current study no relevant differences were detected in heart rate, QRS and QTc duration between the subgroups.

A high pro-BNP level, the presence of a right heart axis and an elevated SPAP on echocardiography are commonly used screening tools for PH and all corresponded with a higher VG-RVPO in limited SSc patients in this study. Pro-BNP is released from the heart in response to wall stress.\textsuperscript{31} This wall stress increases once RV pressure overload develops, causing both an increase in pro-BNP level and an increase in VG-RVPO. Coghlan and colleagues investigated the prevalence of PH in a high risk group of SSc patients and found an independent association between pro-BNP level and PH (estimated coefficient 0.915, P=0.003).\textsuperscript{8} SPAP can be estimated on echocardiography to some extent. For this study an elevated pulmonary pressure on echocardiography was defined as SPAP ≥36 mmHg, which corresponded with an elevated VG-RVPO, both indicating an increase in RV pressures and thereby an increase in wall stress. Furthermore the VG-RVPO was found superior to the presence of a right heart axis as ECG-derived marker for PH. Ahearn and colleagues already showed that conventional ECG parameters are inadequate to rule out PH in this specific patient population, but found the best correlation between a QRS axis >100° in the frontal plane and PH (defined as MPAP >50 mmHg).\textsuperscript{32} A QRS axis >100° is comparable with the presence of a right heart axis (QRS axis >90°). It should however be noted that an MPAP >50 mmHg is a sign of advanced PH and therefore not appropriate for screening of early pulmonary pressure elevation. The heart axis rotates to the right mainly as a result of RV hypertrophy in an advanced stage of PH, whereas the VG-RVPO already changes in response to increased wall stress due to pressure overload in a much earlier stage of the disease.\textsuperscript{11}
This may explain the better performance of the VG-RVPO as compared to the presence of a right heart axis in the detection of PH.

Overall survival after 3 years was 49% for patients with PH in the current study. This is comparable with other studies reporting 3-year survival rates around 50% for this patient population.\textsuperscript{27,33} Once PH was diagnosed in SSc patients, a higher VG-RVPO correlated with increased mortality. An explanation for this finding might be that a higher VG-RVPO corresponds with a higher degree of RV overload and thus a more advanced stage of PH. This implies that the VG-RVPO could potentially be used as marker of prognosis and as indicator to enhance treatment options in this patient population. In previous studies on the prognostic value of ECGs in PH, a decreased survival was reported in PAH patients with a prolonged QRS (≥120 ms) and QTc (≥480 ms) duration.\textsuperscript{34,35} In another study with a heterogeneous population of PH patients a similar association between a low VG on the X-axis (<0 mV.ms) and increased mortality was observed.\textsuperscript{26}

**Limitations**

Our study has some limitations. First, the VG-RVPO could not be computed in 18 out of 291 ECGs (6%), in most cases because of the absence of a clear T wave ending or because of abundant noise on the ECG. None of these 18 patients had PH. Moreover, because of the retrospective nature of this study, previous ECGs were not available for serial analysis in a substantial number of patients. Due to this lack of serial measurements no statement can be made regarding the prognostic value of changes in the VG-RVPO over time in relation to the development of PH. Furthermore, the prevalence of PH was relatively low in our population compared to other literature (7% vs up to 31% in a high risk population with SSc duration more than 3 years and normalized DLCO <60%).\textsuperscript{8} Therefore multivariate analysis could not be performed. Next, the aim of the VG-RVPO is to accentuate the contribution of the right ventricle in the VG vector. However, by forcing the VG in a predefined projection, original information regarding the spatial information which may hold diagnostic information cannot be investigated. Finally, for this study patients were subdivided in the clinical subtypes limited and diffuse SSc to analyse the accuracy of the VG-RVPO per subtype. However, in the latest classification criteria for SSc this subdivision is largely abandoned to increase sensitivity for diagnosing patients with early and limited SSc.\textsuperscript{1} Nevertheless, this study demonstrates that once the diagnosis SSc has been made, the VG-RVPO is sensitive to detect changes in electrocardiographic signal caused by increased wall stress in patients with limited SSc but not in patients with diffuse SSc, making this subdivision clinically relevant for the ECG detection of PH.
**Clinical Implications**

The high prevalence of PH, the implications on prognosis and the benefit of early treatment make screening for PH in patients with SSc mandatory. Conventional parameters such as functional class, conventional ECG, laboratory testing and echocardiography are commonly used to screen SSc patients. The VG-RVPO appears to be an important additional screening parameter, as it is a non-invasive, easy to obtain measurement providing information about pulmonary pressure and prognosis. Moreover, the VG-RVPO can be used to screen for RV overload when echocardiography is inconclusive, for example when tricuspid regurgitation is absent or when image quality is insufficient. The VG-RVPO is generated using the dedicated software program LEADS. The algorithm to compute the VG-RVPO can easily be incorporated in existing software for standard 12-lead ECG analysis.

**Conclusions**

An elevated VG-RVPO is associated with PH in patients with limited SSc and with decreased survival in all SSc patients with PH. Therefore the VG-RVPO has potential as a novel, easy-to-use screening tool for non-invasive PH screening in this population.
References


