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ECG derived ventricular gradient exceeds echocardiography in the early detection of pulmonary hypertension in scleroderma patients

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ABSTRACT

Background: Patients with systemic sclerosis (SSc) are at risk for developing pulmonary hypertension (PH) which is a major cause of death in this population. Echocardiographic (TTE) derived pulmonary arterial pressure (PAP) can be unreliable for the early detection of PH. Previous studies demonstrate that the ECG derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO) can detect PH in a heterogeneous population suspected of PH.

The aim of this study is to assess the use of the VG-RVPO as a screening and monitoring instrument of early PH in SSc patients.

Methods: Serial ECGs and TTEs from twenty-seven SSc patients who underwent right heart catheterization (RHC) were retrospectively analyzed. The changes in PAP and VG-RVPO over time were studied in patients with and without diagnosed PH.

Results: Twenty-four patients (52.5% female, mean age 58.4 years SD 14.3) were studied. In eleven patients PH was confirmed with RHC. In these patients VG-RVPO was significantly higher -8 ± 19 than in patients without PH -23 ± 10 mV·ms, ($P < 0.05$). In addition, in PH patients the VG-RVPO increased over time in contrast to patients without PH ($P < 0.01$). The VG was more sensitive to detect disease progression in earlier stages of disease as compared to echocardiographic derived PAP.

Conclusions: The VG-RVPO is a sensitive, non-invasive and cost effective tool for early detection of PH in SSc patients. Serial measurements indicate that the VG-RVPO can be used as a follow-up instrument and outperforms TTE to detect early changes in right ventricular pressure over time.

1. Introduction

Patients with systemic sclerosis (SSc) have a high risk on developing pulmonary arterial hypertension (PAH) which is a major cause of death in this patient group. The high mortality rates can be partly explained by disease-related comorbidities but also by a relatively late diagnosis in routine clinical practice [1]. Recent cohorts studies show that PH develops in 5–15% of the patients and that early intervention with PAH-targeted therapy is beneficial in patients who are mildly symptomatic [2,3]. Current practice in screening for pulmonary hypertension (PH) in this high risk group mainly relies on symptoms and abnormal findings on transthoracic echocardiography (TTE). In a multicenter study aiming at the development of a screening algorithm in SSc patients (DETECT study), TTE at rest using a sPAP cutoff value of 50 mm Hg and dyspnea as a prominent symptom of PH were not sensitive enough to detect early forms of SSc PH [4,5]. This underlines the need for better screening tools. Progressive PH-related pressure overload of the right ventricle (RV) causes by definition an increase in RV wall tension, and often, but not always, it causes RV hypertrophy and RV dilatation over time [6]. Previous studies show that ECG variables in advanced PH reflect physiologic and anatomic abnormalities in the right ventricle [7]. Thus the ECG may be an important non-invasive, low-cost and easy-to-obtain alternative or extra addition to the other screenings methods. However, the standard 12-lead ECG has only limited value to detect early PAH when conventionally interpreted. Other research demonstrates that the ECG derived ventricular gradient (VG), when projected on the optimal direction for detection of RV pressure overload (VG-RVPO), can detect PH in a heterogeneous population suspected of PH and in patient with SSc [8–10]. It is still unknown

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whether VG-RVPO can be used as a screening instrument for early PH detection, prediction of future PH, and for monitoring its course over time.

In this retrospective study the aim is to assess the value of the ECG-derived VG-RVPO as a follow-up instrument in SSc patients.

2. Methods

The study population consisted of patients with clinically confirmed SSc who underwent right heart catheterization (RHC) between February 2009 and February 2017. Patients took (and still take) part in a care track protocol specialized for SSc and were annually evaluated in the outpatient clinic by a rheumatologist, a cardiologist and a pulmonologist [11]. This includes a standard 10-s 12-lead resting ECG, cardiopulmonary imaging and function tests and clinical evaluation. Patients were included in the study if they had at least 2 consecutive ECGs of good quality and corresponding echocardiograms before and after the RHC. Patients who had prior myocardial infarction were excluded. Annual performance of echocardiography and ECG is part of the care track and performed in all patients. All clinical data were prospectively collected. For the current evaluation selected patients were stratified in 2 groups: patients with and patients without RHC-confirmed PH. Included patients provided written informed consent for use of anonymous clinical data as part of the Biobank Systemic Sclerosis of the department Rheumatology of the LUMC which is approved by the Leiden University Medical Center Institutional Review Board.

2.1. ECG measurements

Standard 10-second 12-lead ECGs were recorded in the supine position. The dedicated software program LEADS (online service: www.leadsecg.com) [12] was used to measure all ECG variables used in this study. LEADS determines conventional ECG variables but also vectorcardiographic ECG variables, after mathematically synthesizing a vectorcardiogram (VCG) from the ECG. One important VCG variable is the ventricular gradient (VG). The VG is defined as the 3D integral of the heart vector over the QT interval. The VG thus gives an indication of the action potential morphology distribution in the heart [9], that changes, due to mechanic-electrical feedback, with changes in right-ventricular afterload [10,13]. Previous research has shown that VG can detect right ventricular pressure overload (and, hence, PH) optimally by taking its projection in the 155° azimuth and 27° elevation direction [10,14]. In the following, this optimized projection of VG is referred to as VG-RVPO (ventricular gradient – right ventricular pressure overload). Within the VCG coordinate system as it has been standardized by the American Heart Association the projection direction of VG-RVPO points to the right, slightly backward, and slightly downward. In normal hearts, VG-RVPO is usually negative, because VG points more in a leftward direction [15]. With increasing right ventricular pressure, the VG turns more rightward, and VG-RVPO becomes less negative, and, for higher degrees of RV pressure overload, even positive. In addition to VG-RVPO, other parameters including heart rate, QTc duration, QRS duration and the heart axis (QRS axis) in the frontal plane were also used in this study.

2.2. Echocardiograms

Images were obtained in the left-lateral decubitus position with a commercially available system (Vivid 7 or E9; General Electric-Vingmed Ultrasound), using a 3.5-MHz transducer, and digitally stored in cine-loop format; offline analysis was performed using EchoPAC version BT 13 (General Electric-Vingmed). Systolic pulmonary pressure (sPAP) was calculated by summation of tricuspid regurgitant gradient (TR) and atrial pressure [16]. sPAP ≥ 34 mm Hg was suspected of having PH. Right atrial pressure was estimated based on the diameter and inspiratory collapse of the inferior vena caval vein IVC [16]. The tricuspid regurgitant jet gradient (TR gradient) was calculated using the modified Bernoulli equation on the 4-chamber view [17].

Included patients had two different primary indications for RHC: risk stratification for hematopoietic stem cell transplantation (HSCT) and screening for pulmonary arterial hypertension, respectively. Patients are excluded for stem cell transplantation if they have pulmonary hypertension. Both groups were discussed in a multidisciplinary team evaluating symptoms and diagnostic test results. Indications for and interpretation of the RHC were done according to the guidelines [18]. Pulmonary arterial hypertension (PAH) (WHO group I) was diagnosed when there was an invasively measured mean pulmonary pressure (mPAP) of 25 mm Hg, a pulmonary arterial wedge pressure of less than15 mm Hg and a pulmonary vascular resistance of >3 woods units [18].

2.3. Statistical analysis

All data was analyzed using SPSS version 23 (SPSS, Chicago, IL). Continuous variables are presented as mean ± SD. Categorical variables are reported as numbers and percentages. To compare continuous variables the unpaired Student *t*-test and Mann-Whitney *U* test were used for respectively normally or non-normally distributed variables. A total of 24 subjects, obtained as 12 in group one and 12 in group two, were each measured at 11 time points. The study achieves 90% power to detect a difference between the (fixed) group means at the last time of 9.00. The standard deviation is 12.00. The correlation between measurements within a subject is 0.500. A test based on a mixed-model analysis is anticipated at a significance level of 0.150.

Linear mixed models analysis was used to assess the differences in change in VG-RVPO and sPAP over time between the two groups [19]. The time points at which ECGs and echocardiograms were made, and at which PH was diagnosed were incorporated in the model as fixed variables. An unstructured covariance matrix was applied. A *P*-value < 0.05 was considered statistically significant.

3. Results

A total of 24 patients (mean age 58 ± 14 years, 62.5% female) were evaluated. PH on RHC was present in 11(45.8%) patients. All patients with the diagnosis PH were classified in WHO group 1 (pulmonary arterial hypertension). The clinical characteristics of the study population at the time of RHC, are displayed in Table 1. The distribution of SSc subtypes in patients with pulmonary hypertension is the same. Among the 24 patients, 12 patients were also known with interstitial lung disease. Patients with PH on RHC had a significantly higher TR gradient and estimated sPAP on echocardiography. Heart rate, QRS duration, QTc duration and the percentage of patients with a right heart axis were not significantly different between the groups. VG-RVPO was significantly higher, less negative or even positive in the PH group.

3.1. VG-RVPO and sPAP over 10 years in pulmonary hypertension versus no pulmonary hypertension

Fig. 1 shows the VG-RVPO and sPAP over 10 years' time. The echocardiographic sPAP over time is depicted in the upper panel of Fig. 1. In the initial phases of the disease (before the RHC) the sPAP on echo of both groups did not differ significantly (95% CI −17.6 to 0, $P = 0.43$). Also after the RHC no significant difference between the PH group and the no PH group were found. The lower panel of the figure contains the VG-RVPO, a more positive VG is associated with higher pulmonary pressures. Overall, the VG-RVPO was significantly higher in patients with PH compared to patients without PH (mean difference −17.3 mV·ms (95% CI −25.6 to −9.1 mV·ms, $P < 0.001$)). Looking closely to the first five years of the disease, that is the years before the RHC, it is noticeable that there is already a significantly higher VG-RVPO in the patients with PH compared to the patients without PH (mean difference −15.0 95% CI −24.0 to −6.2, $P = 0.002$).

4. Discussion

The main finding in this study is that in patients with systemic sclerosis the vector ECG derived ventricular gradient optimized for right

Table 1
Clinical characteristics of the study population at the time instant of RHC.

Variable	No pulmonary hypertension (N = 13)	Pulmonary hypertension (N = 11)	*P*
Age (years)	55.50 ± 16.39	61.88 ± 11.20	0.29
Females (%)	8 (61.5)	7 (63.6)	0.92
Diffuse SSc (%)	9 (69.2)	6(54.5)	0.48
Limited SSc (%)	4 (30.8)	5 (45.5)	0.48
ILD present (%)	5 (38.8)	7 (63.6)	0.23
Echocardiography			
TR Gradient (mm Hg)	25.92 ± 7.68	45.45 ± 18.12	<0.01
Estimated sPAP (mm Hg)	32.31 ± 7.76	49.36 ± 17.37	0.01
LV Dysfunction present (%)	0 (0)	1 (9.1)	0.34
ECG			
Heart rate (bpm)	76.11 ± 16.55	81.48 ± 15.08	0.42
QRS duration (ms)	99.85 ± 19.33	100.73 ± 29.03	0.93
QTc duration (ms)	511.10 ± 60.25	477.50 ± 75.14	0.25
Right heart axis (°)	11.66 ± 72.164	21.9 ± 61.3	0.71
VG-RVPO (mV·ms)	−23.02 ± 10.78	−7.94 ± 18.72	0.02
RHC			
mPAP (mm Hg)	16.85 ± 2.94	28.90 ± 4.70	<0.01

TR, maximum tricuspid regurgitant jet; sPAP, systolic pulmonary arterial pressure; VG-RVPO, ventricular gradient – right ventricular pressure overload. RHC, right heart catheterization. ILD; interstitial lung disease; LV dysfunction: Left ventricular ejection fraction <40%. Data are described as numbers with frequency or mean with SD.

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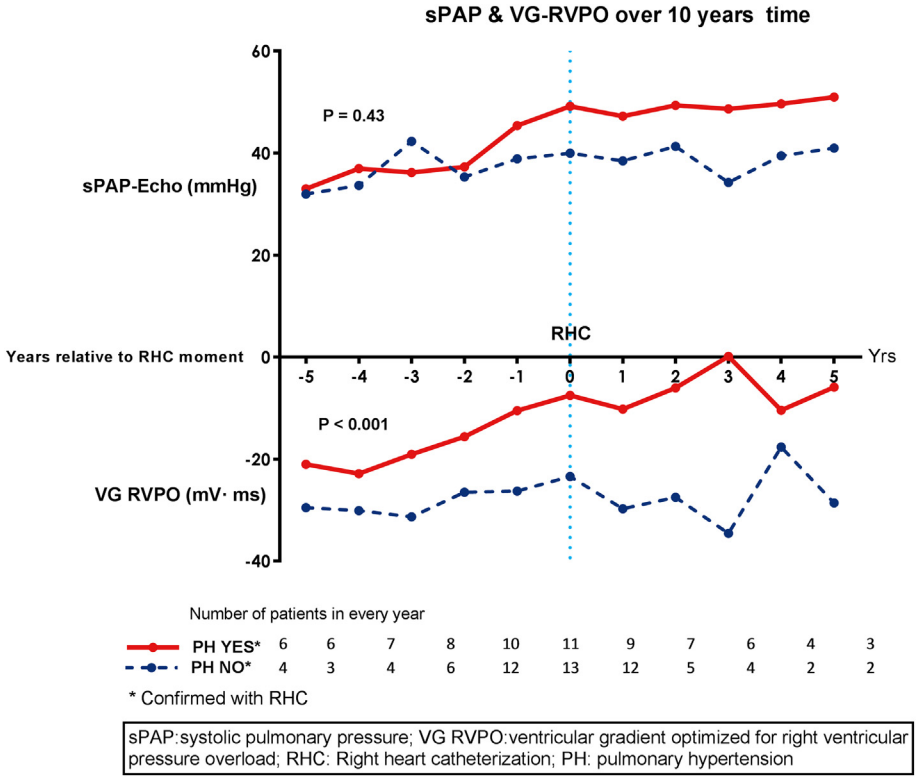

Fig. 1. sPAP & VG-RVPO over 10 year time.

ventricular pressure overload, can play an important role in the monitoring and detection of PH especially in the early phases of the disease.

Current guidelines suggest that early detection and diagnosis of RV dysfunction may help to identify patients with systemic sclerosis who have subclinical PH and might benefit from early treatment [20–23]. Doppler echocardiography is a widely recognized and available tool for monitoring and screening for pulmonary hypertension in various patient groups [24,25]. However the experience of the echocardiographer is crucial and assessment of the RV is complicated [26,27]. The tricuspid gradient may be underestimated if the signal is weak or the regurgitant jet is not fully aligned. This is often the case in early and mild pulmonary hypertension and therefore can be an explanation for the lack of detecting elevated pressures by TTE in our study.

The standard 12 lead electrocardiogram is the most common used non-invasive diagnostic measurement in cardiology. It provides information about frequency, rhythm and conduction disorders. In addition, hypertrophy and fibrosis of both the atria and ventricles can be noticed by changes in depolarization and repolarization. The disadvantage of the standard 12 lead ECG is that it has only a limited value in the early detection of right ventricular overload [28]. One of the reasons is that the conventional ECG criteria are based on detection of right ventricular hypertrophy and this is a late phenomenon of increased pressure overload [29]. In addition, changes in the right ventricle are overshadowed by the much larger left ventricle. Therefore the routine 12-lead ECG is useful for diagnosing left ventricular pathology. A sufficient degree of right ventricular hypertrophy is necessary before the conventional ECG (and QRS) criteria are met, whereas in the early stages of PH the right ventricular wall tension is increased while hypertrophy has not developed yet [30,31].

There are more ECG-variables to detect increased right ventricular pressure [8,31,14,32–34]. These variables can easily be calculated from a digitally stored 12 lead ECG after transforming them into a VCG. The VCG analysis programs, like our LEADS program, that is available as an online service, can calculate the VG as used in our study. Actually, the VG is a measurement that includes the entire QRST complex. When right-ventricular pressure increases, there is an immediate T-wave change that reflects right-ventricular strain, and this change becomes evident in the ventricular gradient. Previous research has shown that the magnitude and direction of this ventricular gradient when projected in the optimal direction to detect RV overload is a specific marker for the presence and the severity of right ventricular overload. Couperus et al. already stated that also in patients with systemic sclerosis the ventricular gradient optimized for right ventricular pressure overload is significantly elevated when they have pulmonary hypertension [14]. The current study confirms this once more and also makes a distinction in the early phase of the disease between patients who develop PH and who not.

All patients in this study were classified in WHO group 1 (pulmonary arterial hypertension), however pulmonary fibrosis is also a leading cause of death in SSc patients [35,36]. In our cohort 12 patients presented with interstitial lung disease. There is little literature available on ECG changes in interstitial lung disease. The right side of the heart attempts to deal with the progressive loss of vascular bed, as a result it hypertrophies [37]. Impaired gas exchange in ILD leads to important desaturation and vital organs such as the heart have a decreased oxygen delivery [38]. It is imaginable that those changes influence the ECG (and VG-RVPO). In future research the impact of interstitial lung disease on the electrocardiogram must be taken into account.

5. Conclusion

The VG-RVPO is a sensitive, non-invasive and cost effective tool for early detection of pulmonary hypertension in SSc patients. Moreover serial measurements indicate that the VG-RVPO can be used as a follow-up instrument and outperforms TTE to detect early changes in right ventricular pressure over time.

6. Limitations

Due to the retrospective nature of this study, not every ECG or echocardiogram was available at every timepoint. We only have data on a

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small number of patients; due to low prevalence of the disease and the strict requirements for performing an RHC. Despite these small numbers there still is a significant result which underlines the relevance and additional value of the VCG.

Conflict of interests

The Department of Cardiology receives unrestricted grants from Actelion Pharmaceuticals Nederland BV (Woerden, the Netherlands), Biotronik (Berlin, Germany), Boston Scientific (Natick, Massachusetts) and Medtronic (Minneapolis, Minnesota). The software was developed by C.S. and H.V. and launched for general use by Fysiologic ECG services. C.S. and H.V. are still involved in this company (www.leadsecg.com).

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