Characterization of the right ventricle : embryonic development, noninvasive imaging and electrocardiography

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Chapter 12

Diagnosis and Mortality Prediction in Pulmonary Hypertension: The Value of the ECG-derived Ventricular Gradient

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ABSTRACT

Purpose

The aim was to investigate the use of the ECG-derived ventricular gradient, projected on the x-axis (VGx), for detection of pulmonary hypertension (PH) and for prediction of all-cause mortality in PH patients.

Methods

In patients referred for PH screening (n=216), the VGx was calculated semi-automatically from the ECG and was defined as abnormal when <24 mV·ms. The VGx of PH patients was compared to the VGx of patients without PH. The association between a reduced VGx and mortality was investigated in PH patients.

Results

PH patients (n=117) had a significantly reduced VGx:14 ±27 vs. 45 ±23 mV·ms, p<0.001. Furthermore, a severely reduced VGx (<0 mV·ms) was associated with increased mortality in PH patients: hazard ratio 1.025 (95% CI 1.006 – 1.045, p=0.012), per mV·ms VGx decrease.

Conclusion

Reduced VGx is associated with the presence of PH and, more importantly, within PH patients, a severely reduced VGx predicts mortality.

INTRODUCTION

Pulmonary hypertension (PH) is an uncommon, but serious disease, characterized by a mean pulmonary artery pressure (MPAP) ≥25 mm Hg.[1] PH can be due to a primary disease process in the pulmonary arteries, referred to as pulmonary arterial hypertension (PAH).[2,3] Furthermore, PH can be secondary to e.g. left sided heart disease, pulmonary parenchyma abnormalities, thromboembolic occlusion of the pulmonary arteries or other diseases that lead to pulmonary vascular abnormalities.[2,3] As PH is a progressive disease, irrespective of the cause, timely detection and treatment is necessary to improve symptoms and prognosis.[4–6] However, symptoms are generally mild until advanced stages of the disease and regular screening for PH is frequently required, specifically in patients who are at risk for developing PAH (e.g. patients with inflammatory connective tissue diseases, portal hypertension, or congenital heart disease).[7] Currently, the gold-standard for PH screening is echocardiography, in which the systolic pulmonary artery pressure (SPAP) is derived through estimation of the peak systolic right ventricular pressure.[8] Recently, the vectorcardiogram (VCG), synthesized from the standard 12-lead ECG, demonstrated to be of use for detection of elevated right ventricular (RV) pressure as a consequence of PH. In a case-control study, the ECG of patients with idiopathic PAH was compared to the ECG of matched healthy subjects.[9] In that study, the ventricular gradient (VG) vector projected on the x-axis (VGx) was strongly associated with pulmonary artery pressure. It was shown that the VGx has a positive value in healthy subjects and steadily reduces to zero or becomes negative with increasing RV afterload. In addition, the VGx demonstrated to have a higher diagnostic accuracy for detecting elevated RV pressure, than other ECG and VCG parameters. This indicated that quantitative ECG screening could be a valuable tool for the recognition of elevated pulmonary pressure in suspected idiopathic PAH patients. However, it remained to be investigated whether the observations were also applicable in the regular patient population of suspected PH patients, in which comorbidity is common.[10] In addition, the association between a reduced VGx and patient survival was not investigated. Therefore, we investigated whether quantitative ECG screening with the VGx, could also be applied in the more heterogeneous patient population that is regularly referred for PAH screening. Furthermore, the association of a reduced VGx and all-cause mortality was assessed.

MATERIALS AND METHODS

Consecutive patients who were referred for diagnosis and treatment of suspected PAH were included in the current analysis. First, all patients underwent the standard noninvasive screening protocol for PAH according to the international guidelines.[11,12] As part of this protocol, a 10s, 12-lead electrocardiogram (ECG) was obtained and echocardiography was performed.

Second, if the noninvasive screening protocol indicated the presence of PAH or when the absence of elevated pulmonary artery pressure could not be established, right heart catheterization was performed. Thus, through combination of the results from the noninvasive screening protocol and right heart catheterization, the final PH diagnosis was established and patients were categorized into five different groups according to the WHO classification for PH etiology. Treatment was initiated subsequently, and the patients with PH were followed regularly during out-patient clinic visits according to current guidelines.[10,13,14] Patients with PAH were followed-up every three months, specifically when PAH-aimed therapy was initiated. Patients with other PH etiologies were followed less frequently, however at least bi-annually. For the purpose of the current evaluation; all-cause mortality was noted during follow-up.

Electrocardiography

The ECGs were first stored digitally, thereafter exported from the ECG database management system and analyzed with the MATLAB-based (The MathWorks, Natick, MA) computer program LEADS (Leiden, the Netherlands). Details on the technical background of LEADS have been reported previously.[15] In short, the standard 10s ECG was averaged into one single beat that was subsequently converted into a vectorcardiographic beat in a largely automated process. Besides heart rate, QRS duration and QT interval (corrected for heart rate according to the Fridericia formula), the software quantitated the magnitude and orientation of the mean QRS and T integral vectors, defined as azimuth (horizontal vector orientation, in degrees) and elevation (vertical vector orientation, in degrees).[16] Thus, the angle between QRS and T vectors, the QRS-T angle was calculated and ventricular gradient vector, including the projection of the VG vector on the x-axis (VGx), was derived (see Figure 1).[9] In a previous study, it was demonstrated that normal subjects had a VGx of 24 mV·ms or higher.[9] Therefore, with the purpose to analyze this cut-off value in a clinical context, the current patient population was subdivided into a group with a VGx <24 mV·ms and a group with a VGx ≥24 mV·ms.

Echocardiography

Imaging took place in the left lateral decubitus position on a commercially available system (Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin). Regular images were obtained and specific attention was addressed to the measurement of the RV to RA pressure gradient or tricuspid regurgitant jet gradient (TR gradient) and the derived estimation of the SPAP.[8] The estimated SPAP was defined as the RV to RA pressure gradient added to the right atrial pressure. Right atrial pressure was estimated 5 mmHg to 15 mmHg, according to

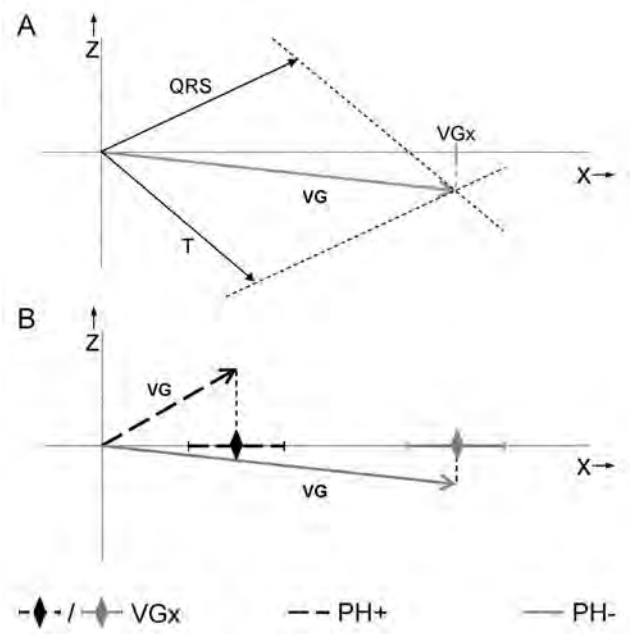

Figure 1. Orientation and size of the ventricular gradient. Panel A: The ventricular gradient is the resultant vector of the QRS and T integral vector, which have the same orientations as the regular QRS and T axes. Panel B: The ventricular gradient projected on the x-axis (VGx) previously demonstrated to be reduced in patients with idiopathic pulmonary arterial hypertension (dashed vector) as compared to healthy subjects (grey vector).(9) Positive X direction: right-to-left; positive Y direction: anterior-to-posterior.

the diameter and inspiratory collapse of the inferior caval vein.[17] If adequate measurement of the TR gradient could not be obtained in the apical 4 chamber position, the measurement was repeated in the short-axis view at the level of the aorta and, if necessary, in the subcostal view. If this still did not result in adequate measurement of the TR gradient, agitated saline was used to improve the signal intensity of the tricuspid regurgitant jet.[14]

Right heart catheterization

Right heart catheterization was performed according to the international guidelines for invasive hemodynamic assessment of PAH.[18] For the current analysis, the SPAP, the diastolic pulmonary artery pressure (DPAP) and the mean pulmonary artery pressure (MPAP) were used. Measurements were obtained with the patient in supine position with a Swan-Ganz catheter placed in the pulmonary artery.

Statistical analysis

To investigate how elevated pulmonary pressure was reflected in ECG changes, Pearson correlation coefficients were determined between ECG characteristics and the echocardiographically estimated SPAP, which is currently the gold-standard for noninvasive pulmonary pressure estimation. Furthermore, the odds ratio of a VGx <24 mV·ms as compared to ≥24 mV·ms, was calculated for the presence of an estimated SPAP ≥40 mmHg, which corresponds to the echocardiographical diagnosis of pulmonary hypertension. In addition, the odds ratio of an abnormal VGx was calculated for the final diagnosis of PH, which was established after patients completed the noninvasive screening protocol and, if necessary, right heart catheterization. Furthermore, a receiver operating characteristic (ROC) curve analysis was performed, to determine the diagnostic accuracy of the above-described VGx cut-off (<24 mV·ms) and three other cut-off levels (30, 35 and 40 mV·ms). Thereafter, the 3-year survival characteristics were investigated in patients with PH. For this purpose, univariate and multivariate (adjusted for sex, age, heart rate and WHO PH classification) Cox's proportional hazard regression analysis was performed, in which the VGx was entered into the regression equation as a continuous variable. It was previously noted that PAH patients with most extensive RV disease typically present with a VGx <0 mV·ms.[9] Therefore, all-cause mortality Kaplan Meier curve of patients with a VGx <0 mV·ms was compared to the Kaplan Meier curve of patients with a VGx ≥0 mV·ms. A logrank test was performed to assess whether the survival curves differed significantly between both groups.

Where appropriate, continuous variables are reported as mean ± SD, binary logistic and Cox's proportional hazard regression coefficients are reported with 95% confidence interval. A p-value <0.05 was considered statistically significant.

RESULTS

General and disease specific characteristics of the patient population

A total of 216 patients (82 male, 38.8%) were screened for the presence of PAH. Overall the average age was 54.6 ±16.4 years at the time of screening. After initial noninvasive screening 143 patients were suspected of PH (see Figure 2), mainly due to an elevated SPAP (≥40 mmHg) as estimated echocardiographically (n=114). In 29 of the 143 patients, there was no echocardiographical evidence for PH. Nonetheless, a high suspicion of PAH was present in these patients, as a consequence of the severity of symptoms, as a result of abnormal functional tests or due to radiological findings.

From the group of 143 suspected PH patients, 89 underwent right heart catheterization. Right heart catheterization was not performed in the remaining 54 patients in whom an

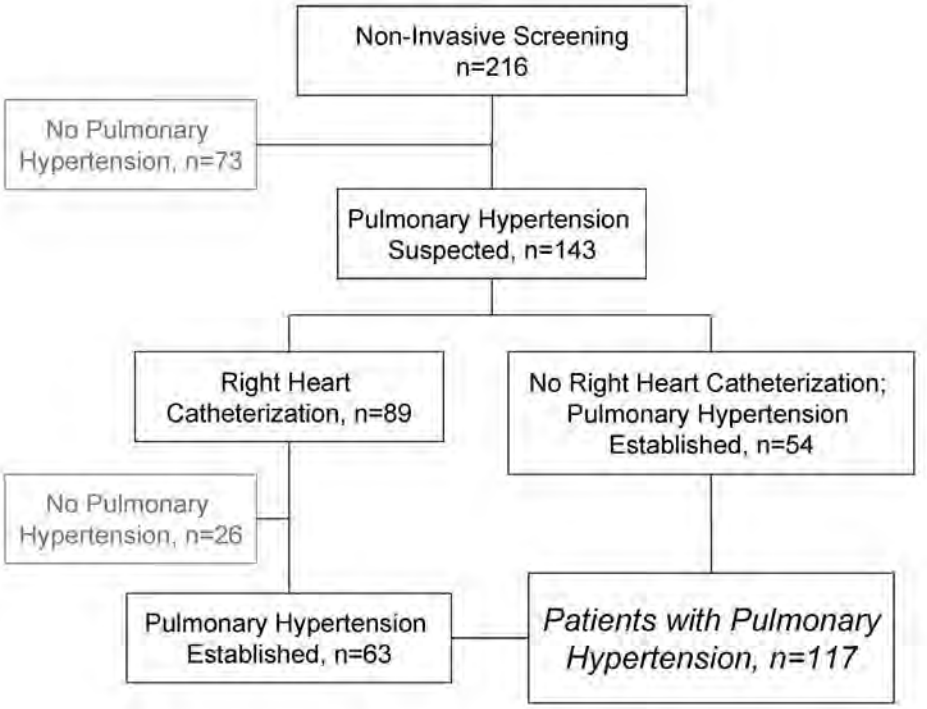

Figure 2. Results of the screening algorithm for patients suspected of PAH. In total, 216 patients were screened noninvasively. After noninvasive screening, 143 patients were suspected of PH and 73 patients had no PH. In 89 patients, suspected of PAH, right heart catheterization was performed, which confirmed PH in 63 patients. After noninvasive screening and right heart catheterization, PH was diagnosed in 117 patients.

elevated SPAP was found echocardiographically. This group consisted of patients with clinically and echocardiographically established Eisenmenger syndrome, or patients in whom left sided heart failure was undisputable and right heart catheterization would have no further therapeutic consequences.

After noninvasive screening of all patients, and right heart catheterization in the patients in whom it was indicated, PH was diagnosed in 117 patients. The characteristics of these patients are listed in Table 1. In 49 patients (42%) WHO group I (previously referred to as primary pulmonary hypertension) was diagnosed. Left ventricular or valvular disease and hypoxic lung disease were other frequently occurring causes of pulmonary hypertension (Table 1).

Electrocardiographic diagnosis of elevated pulmonary pressure

The ECG parameters are summarized in Table 2. PH patients had a higher heart rate, a longer QRS-duration and QTc-interval as compared to patients without PH. Furthermore, the angle

Table 1. Patient characteristics.

	No pulmonary hypertension (n=99)	Pulmonary hypertension (n=117)	P
Clinical characteristics			
Age (years)	54.1 ± 15.4	55.9 ± 16.1	0.405
Range	22.4-80.0	17.4-94.1	
Sex (male/female)	39/60	43/74	0.690
Functional class (NYHA)	1.9 ± 0.8	2.6 ± 0.7	<0.001
Main risk factor for developing PH (n)			
Congenital systemic-pulmonary shunt	5	35	
Connective tissue disease	27	7	
Auto-immune disease	2	5	
Liver Cirrhosis	9	4	
Pulmonary embolism	23	6	
Hypoxic lung disease	13	20	
Left ventricular/valvular disease	5	30	
Other or no specific risk factor	15	4	
Echocardiography			
Estimated SPAP (mmHg)	31 ± 9	61 ± 20	<0.001
Right heart catheterization	**26**	**63**	
SPAP (mmHg)	27 ± 6	65 ± 21	<0.001
DPAP (mmHg)	11 ± 4	27 ± 13	<0.001
MPAP (mmHg)	17 ± 4	40 ± 13	<0.001
WHO PH classification		**117**	
I (%)		49 (42%)	
II (%)		31 (26%)	
III (%)		14 (12%)	
IV (%)		6 (5%)	
V (%)		3 (3%)	
Combined (%)		14 (12%)	

DPAP: diastolic pulmonary artery pressure; MPAP: mean pulmonary artery pressure; PH: pulmonary hypertension; SPAP: systolic pulmonary artery pressure. Numbers correspond to n, unless mentioned otherwise.

between the de- and repolarization vector, or QRS-T angle, was significantly wider. However, as compared to the other ECG and VCG parameters, the most prominent difference between PH patients and patients without PH was observed in the VGx, which was significantly lower in PH patients. A less pronounced VGx difference between patients with and patients without PH, was observed in those who either had a history of left sided heart disease or a history of a WHO group V-related disease (e.g. sarcoidosis) (see Figure 3).

The correlations between the SPAP, as estimated with echocardiography, and the ECG parameters are summarized in Table 2. The VG vector demonstrated to be inversely correlated with the estimated SPAP, as was the VGx, which demonstrated the strongest correlation with the SPAP (R=-0.64, p<0.001). The negative correlation denoted that an increasing SPAP was associated with a decreasing VGx. Hence, a reduced VGx represented an elevated SPAP.

To further explore the clinical applicability of the VGx, patients with an abnormal VGx (<24 mV·ms) were compared to patients with a normal VGx. Thereafter, the odds ratio of having a

Table 2. ECG characteristics.

	No pulmonary hypertension (n=98)	Pulmonary hypertension (n=117)	P	R estimated SPAP (n=203)	P
Heart rate (bpm)	72 ± 13	79 ± 17	<0.001	0.17	0.016
QRS duration (ms)	93 ± 22	102 ± 25	0.007	0.22	0.002
QTc interval (ms)	403 ± 33	417 ± 40	0.004	0.27	<0.001
Mean QRS vector magnitude (μV)	352 ± 175	397 ± 219	0.102	0.24	0.001
QRS axis azimuth (°)	38 ± 45	37 ± 90	0.925	-0.15	0.036
QRS axis elevation (°)	15 ± 24	13 ± 36	0.608	-0.09	0.219
Mean T vector magnitude (μV)	164 ± 76	153 ± 112	0.399	-0.02	0.881
T axis azimuth (°)	-40 ± 32	-11 ± 75	<0.001	0.36	<0.001
T axis elevation (°)	20 ± 17	16 ± 29	0.198	0.04	0.569
QRS-T angle (°)	83 ± 36	111 ± 43	<0.001	0.33	<0.001
Ventricular gradient magnitude (mV*ms)	59 ± 25	41 ± 22	<0.001	-0.34	<0.001
Ventricular gradient azimuth (°)	-6 ± 33	24 ± 73	<0.001	0.20	0.004
Ventricular gradient elevation (°)	26 ± 17	22 ± 30	0.315	0.01	0.839
Projection of VG on x-axis (mV*ms)	44 ± 23	14 ± 27	<0.001	-0.64	<0.001

Azimuth: horizontal vector orientation (degrees), Elevation: vertical vector orientation (degrees).

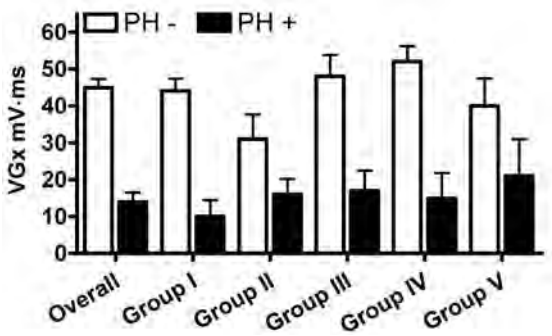

Figure 3. Mean VGx according to patient history. Patients were subdivided into different groups according to the world health organization classification for pulmonary hypertension etiology. Group I refers to primary forms of pulmonary arterial hypertension. Patients in group II have a history of left sided heart disease. Patients in group III have a history of pulmonary disease. Group IV refers to a history of pulmonary embolism. Group V is the miscellaneous category and mostly existed of patients with sarcoidosis. Mean and SEM were plotted to visualize the differences in VGx between patients with and patient without pulmonary hypertension (PH).

reduced VGx for the presence of elevated pulmonary pressure, was calculated. Patients with a reduced VGx (<24 mV·ms, n=97), exhibited an odds ratio of 11.3 (95% CI 5.7 – 22.3, p<0.001) for the echocardiographic diagnosis of PH, as compared to patients with a normal VGx. Exclusion of patients with a history of left sided heart disease, resulted in an odds ratio of 17.4 (95% CI 7.5 – 40.5, p<0.001) Furthermore, in patients with a reduced VGx, the odds ratio for the presence of the final PH diagnosis, which was established after patients completed the noninvasive diagnostic algorithm and (if necessary) right heart catheterization, was 7.9 (95%

CI 4.2-14.7, p<0.001). For the final PH diagnosis, the odds ratio was 9.0 (95% CI 4.4 – 18.4, p<0.001), when patients with a history of left sided heart disease were excluded.

ROC curve analysis was done to study the diagnostic performance of the VGx for the detection of elevated SPAP as estimated with echocardiography and for the final diagnosis of PH, which was established with noninvasive screening and right heart catheterization (Table 3). The application of the VGx for detection of an elevated SPAP as estimated with echocardiography, revealed an area under the curve of 0.83 (p<0.001). The 24 mV·ms cut-off, was associated with a sensitivity of 70% and a specificity of 83%. A VGx cut-off of 40 mV·ms yielded a sensitivity of 87% and a specificity of 61%. Exclusion of patients with a history of left sided heart disease increased the area under the curve to 0.88 (p<0.001). Whereas the 24 mV·ms cut-off was associated with a sensitivity of 73% and a specificity of 85% after exclusion of patients with left sided heart disease, the 40 mV·ms cut-off had a sensitivity of 90% and a specificity of 67% (Table 3).

Table 3. Diagnostic accuracy of different VGx cut-offs.

	WHO group II patients included				WHO group II patients excluded			
	Sens (%)	Spec	PPV	NPV	Sens	Spec	PPV	NPV
Estimated SPAP ≥40mmHg								
< 24 mV·ms	71	81	81	70	73	85	85	73
< 30 mV·ms	77	79	81	75	79	83	85	77
< 35 mV·ms	82	69	76	77	83	73	78	79
< 40 mV·ms	87	61	72	80	90	67	76	85

Numbers correspond with percentage. NPV: negative predictive value; PH: pulmonary hypertension; PPV: positive predictive value; Sens: sensitivity; SPAP: systolic pulmonary artery pressure; Spec: specificity.

Mortality risk and VGx

During a three year follow-up of the PH patients (n= 117), 23 patients (19.7%) died. The average follow-up time was 21.8 ±13.1 months. Univariate survival analysis revealed that a reduced VGx was significantly associated with the increased incidence of all-cause mortality. The crude hazard ratio was 1.018 (95% CI 1.003 – 1.034, p=0.020), per mV·ms decrease in VGx. After multivariate correction for age, sex, heart rate and WHO classification group, the hazard ratio was 1.025 (95% CI 1.006 – 1.045, p=0.012) per mV·ms decrease in VGx.

In patients with a VGx ≥0 mV·ms, survival was 88% at one year and 84% at three years (figure 4). In patients with a VGx <0 mV·ms, which is associated with more severe RV pressure overload, survival was 77% at one year and 66% at three years. This resulted in a 20% three-year survival difference between patients with a VGx <0 mV·ms as compared to patients with a VGx ≥0 mV·ms, logrank p=0.02 (Figure 4).

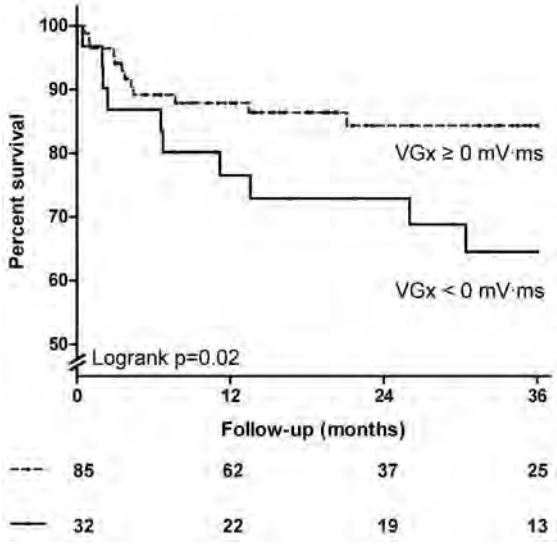

Figure 4. Survival characteristics in PH patients. The dashed line depicts the survival characteristics of patients with a VGx ≥0 mV·ms. The solid line indicates patients with a VGx <0 mV·ms, which previously has been associated with severe right ventricular pressure overload. The numbers below signify patients at risk per group.

DISCUSSION

Key findings were that:[1] the VGx correlated inversely with pulmonary pressure,[2] an abnormally reduced VGx showed a prominent association with the presence of PH,[3] a severly decreased VGx was related with increased mortality in patients with PH.

In a recent study on normal subjects and patients with idiopathic forms of PH, it was demonstrated that a reduced VGx was related to elevated pulmonary pressures and to increased right ventricular mass and size.[9] In the current analysis, in which patients with various forms of PH were included, a similar association between the VGx and elevated pulmonary pressures was observed. The VGx correlated inversely with the peak right ventricular pressure as estimated with echocardiography, and the risk of PH was significantly elevated in patients with an abnormally reduced VGx (<24 mV·ms).

PH causes elevated RV wall stress and leads to right ventricular hypertrophy as a consequence of RV remodeling. Both increased wall stress as well as hypertrophy, result in ECG changes. The extent and visibility of those changes depends on the height of the pulmonary pressure and on the degree of right ventricular remodeling, but also on the ECG parameter that is used. Classic 12-lead surface ECG criteria rely on depolarization characteristics that relate to RV hypertrophy. Unfortunately, RV hypertrophy is a relatively late phenomenon that becomes apparent in advanced stages of PH. Therefore regular surface ECG-derived criteria are not well suited for early detection of increased pulmonary pressure. Previous studies

demonstrated that VCG criteria, specifically the criteria that also incorporate repolarization characteristics, can more reliably detect elevated pulmonary pressure, also in earlier stages of the disease.[19–22] In another study, diagnostic performance of standard ECG criteria was compared to VCG criteria, including the VGx, in a homogeneous population of idiopathic PAH patients.[9] This demonstrated that the T-integral vector was more affected in terms of magnitude and orientation as compared to the QRS-integral vector. Nonetheless, the VG vector, which incorporates de- and repolarization had the best diagnostic accuracy for the detection of RV overload. The current evaluation confirmed these findings in a heterogeneous population of patients who were referred for PAH screening. The best correlations were observed between the pulmonary pressure and the VCG parameters that incorporated de- and repolarization characteristics, such as the ventricular gradient. A VGx <24 mV·ms, which was the lower limit of a normal VGx in the study by Henkens et al., demonstrated to be associated with an almost 8-fold increased risk for the presence of idiopathic PH as compared to patients with a normal VGx. In the current study, an odds ratio of 7.9 was found for an VGx <24 mV·ms, which is comparable to results of the study of Henkens et al.[9]

The VG, defined as the QRST integral, can be calculated on the standard ECG as well as the VCG and represents the heterogeneity in action potential durations within the heart.[23] Previous studies have shown that RV overload causes distinct alterations in QRS and T vectorloops. Cowdery et al. indicated the implications of a hypertrophic RV for the QRS vectorloop and Kawaguchi and colleagues showed the value of the T vector loop-area.[21,24] PH and resultant RV overload is associated with a relatively lower contribution of LV electrical forces. As a consequence, the VG vector reduces in magnitude and becomes oriented more posteriorly (see Figure 1). Both these characteristics are reflected in the projection of the VG on the x-axis, or VGx. Thus, the VGx is a surrogate measure, optimal for detection of RV overload as demonstrated by the current and previous evaluations.[9,22]

The present study is the first in which the association between a reduced VGx and unfavorable survival characteristics is demonstrated. In both the univariate as well as the multivariate analysis, a reduced VGx was significantly associated with the increased incidence of all-cause mortality. In patients with PH, irrespective the cause, reduced RV function is an important predictor of mortality.[25,26] Patients with a reduced VGx, who have more elevated right ventricular pressure as compared to patients with a normal VGx, are likely to have more impaired RV function. Therefore, a reduced VGx probably identifies the patients who have decreased RV function and exhibit worse survival as compared to patients with a higher VGx. The findings in the current study underscore this concept.

Clinical implications

The ECG-derived VGx could be a good screening tool for PH in high risk groups, e.g. patients with pulmonary disease and chronic hypoxemia, or patients with inflammatory connective tissue diseases. Routine ECG analysis during out-patient clinic visits can be used as an initial PH screening, specifically in these risk groups. Referral for echocardiography and further analysis could be considered as soon as a reduction of VGx occurs. Nowadays, timely detection is even more important, because early treatment demonstrated to be beneficial in patients with PAH.[6]

Currently, several treatment modalities are available for patients with PAH. Potentially, a therapy-induced reduction in pulmonary vascular resistance and decrease in RV overload may be reflected by increased VGx. Therefore, further studies should assess the association between treatment effect and changes in VGx magnitude. Besides the application of the VGx for PH screening and treatment follow-up, the VGx can also be applied to identify patients who are at increased risk of all-cause mortality, in whom a more aggressive treatment regimen may be required. This however has to be confirmed in clinical trials.

Limitations

In the present analysis, the VCG was derived from the standard ECG using the semi-automated computer program LEADS, which is a non-commercially available tool for computerized ECG analysis. Currently, electrocardiographs do not provide the VGx, thus it has to be calculated afterwards using dedicated software. Nonetheless, only limited additions to the ECG analysis software would be required to provide the VGx fully automatically.

CONCLUSION

A reduced VGx identifies patients with elevated pulmonary artery pressure in a heterogeneous population of patients suspected of pulmonary arterial hypertension. More importantly, a severly reduced VGx is associated with increased all-cause mortality risk in patients with pulmonary hypertension.

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