Improved ECG detection of presence and severity of right ventricular pressure load validated with cardiac magnetic resonance imaging

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Methods

The study aimed to assess whether the 12-lead ECG-derived ventricular gradient, a vectorial representation of ventricular action potential duration heterogeneity directed toward the area of shortest action potential duration, could improve ECG diagnosis of chronic right ventricular (RV) pressure load. ECGs from 72 pulmonary arterial hypertension patients recorded <30 days before onset of therapy were compared with ECGs from matched healthy control subjects (*n* = 144). Conventional ECG criteria for increased RV pressure load were compared with the ventricular gradient. In 38 patients a cardiac magnetic resonance (CMR) study had been performed within 24 h of the ECG. By multivariable analysis, combined use of conventional ECG parameters (rsr’ or rsR’ in V1, R/S > 1 with R > 0.5 mV in V1, and QRS axis > 90°) had a sensitivity of 89% and a specificity of 93% for presence of chronic RV pressure load. However, the ventricular gradient not only had a higher diagnostic accuracy for chronic RV pressure load by receiver operating characteristic analysis [areas under the curve (AUC) = 0.993, SE 0.004 vs. AUC = 0.945, SE 0.021, *P* < 0.05], but also discriminated between mild-to-moderate and severe RV pressure load. CMR identified an inverse relation between the ventricular gradient and RV mass, and a trend toward a similar relation with RV volume. In conclusion, chronically increased RV pressure load is electrocardiographically reflected by an altered ventricular gradient associated with RV remodeling-related changes in ventricular action potential duration heterogeneity. The use of the ventricular gradient allows ECG detection of even mildly increased RV pressure load.

Hypertension; pulmonary; right ventricular hypertrophy; diagnosis; ventricular gradient; electrocardiogram

Mildly increased chronic right ventricular (RV) pressure load is hard to detect noninvasively because of the position and mass of the RV (7, 13, 23). Conventional 12-lead ECG parameters of increased RV pressure load lack diagnostic accuracy, precluding their use for screening purposes (3, 16, 26, 31, 34), partly because the chest electrodes predominantly overlie the left ventricle (LV) and partly because the 12-lead ECG renders 12 separate one-dimensional projections of the three-dimensional (3-D) cardiac vector in time (25), but not in the least because the RV mass is relatively low compared with the LV mass. This scalar ECG representation hampers the direct appreciation of the ECG as a recording of a 3-D process. However, a synthesized vectorcardiogram can be easily derived mathematically from the ECG, allowing the calculation of electrocardiographic 3-D parameters. One of these parameters is the ventricular gradient (VG), a 3-D measure of ventricular action potential duration (APD) heterogeneity oriented from the area with the longest APD toward the area with the shortest APD (11, 18). The VG (mV·ms) is the sum of the 3-D integrals of both the QRS complex and the T wave (net area subtended by the heart vector over the QRS complex and the T wave) (11, 18). A change in magnitude and/or orientation of the VG signifies a change in APD heterogeneity (11, 19). APD changes due to chronic RV pressure load must therefore change the VG (19). In a rat model, we recently demonstrated that the VG changes markedly during the development of pulmonary arterial hypertension (PAH), a model of chronic RV pressure load (17). We therefore decided to study the use of the VG in diagnosing chronic RV pressure load in humans, however, comparison of ECGs at the time of diagnosis of PAH with ECGs from a disease-free state is, in general, not feasible, since PAH remains undetected for a long time (22). ECGs from PAH patients were therefore compared with ECGs from healthy controls. To further appreciate the diagnostic potential of the VG in chronic RV pressure load, all ECGs were also evaluated for the conventional criteria of increased right heart load (27).

Methods

Patients. The study complies with the Declaration of Helsinki. Patient data were gathered as part of routine clinical care in the VU University Medical Center and were analyzed retrospectively. Healthy control subjects gave written informed consent for the present study, which was approved by The Institutional Ethical Review Board of the Leiden University Medical Center.

Between December 1999 and December 2005, 565 consecutive patients were evaluated with a right heart catheterization because of suspected PAH, defined as a mean pulmonary artery pressure (PAP) >25 mmHg and pulmonary capillary wedge pressure <15 mmHg. PAH was considered to be idiopathic when identifiable causes for pulmonary hypertension (i.e., congenital heart disease, portal hypertension, collagen vascular disease, HIV infection, left heart disease, hypoxic pulmonary disease, or chronic thromboembolic disease) were excluded (3, 14). One hundred ten patients were identified with idiopathic PAH. A digitally stored ECG recorded within 30 days before diagnostic right heart catheterization was available in 72 patients (15 male).

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The VG is defined as:
spatial orientation (azimuth°, orientation in the transversal plane, and mixed venous SpO2,% 63 10 blood.
Cardiac index, l
RAP, mmHg 9 6
Pulmonary vascular resistance (in mmHg
Oxygen consumption was measured during right heart catheterization. Cardiac output was calculated using Fick’s principle.
mixed venous oxygen saturation were measured. Cardiac output was calculated using Fick’s principle. Oxygen consumption was measured during right heart catheterization. Pulmonary vascular resistance (in mmHg x t) is the heart vector, as represented in the X, Y, and Z leads of the vectorcardiogram (5). This integral, the T-wave integral, and the VG is illustrated in the signal quality criteria (baseline, noise). This selection of beats is then averaged by LEADS. After manually reviewing and editing the onset and end of the QRS complex, a synthesized vectorcardiogram is generated with the inverse Dower matrix (10, 12). Parameters derived from this vectorcardiogram, such as the VG magnitude (mV·ms) and spatial orientation (azimuth°, orientation in the transversal plane, and elevation°, deviation from the transverse plane), are then calculated. The VG is defined as: \( \int \hat{H}(t) \, dt \), in which \( \hat{H}(t) \) is the heart vector, as represented in the X, Y, and Z leads of the vectorcardiogram (5). This integral, taken over the QRSST interval, is nonzero due to action potential morphologic differences in the ventricles, most often thought of as APD differences (11). Orientation of the axes is in accordance with the American Heart Association recommendations: x-axis positive from right to left, y-axis positive in craniocaudal direction, and z-axis positive in anteroposterior direction (24). Control ECGs were selected from a large database of healthy students of the Leiden University Medical Faculty. All ECGs were scrutinized for normality according to the Minnesota criteria by an experienced cardiologist (4). Prior to the use of the selected ECGs for comparison in this study, all ECGs were anonymized. All ECGs were analyzed twice by the first author (I. R. Henkens), and a third time by the second author (K. T. B. Mouchaers) to determine the intraobserver and interobserver variability for calculating the VG. Because the VG depends on heart rate (38) and sex, but not on the pressure scale is set at 0 –100 mmHg in the patients with moderate and severe PAH. Of note is that the pressure scale is set on different levels of chronic right ventricular (RV) pressure load on the ECG and vectorcardiogram is illustrated in a patient without pulmonary arterial hypertension (PAH) (catheterized for exclusion of familial PAH after inconclusive transthoracic contrast echocardiography; left), a patient with moderate PAH (middle), and a patient with severe PAH (right), respectively. Top panels: RV and pulmonary artery (PA) pressures (PAP). Horizontal lines, mean PAP. Mean PAP = 11 mmHg in the patient with PAH. Mean PAP = 43 mmHg in the patient with moderate PAH. Mean PAP = 64 mmHg in the patient with severe PAH. Of note is that the pressure scale is set at 0–20 mmHg in the control subject with normal RV pressure load, whereas the pressure scale is set at 0–100 mmHg in the patients with moderate and severe PAH. Second row panels: corresponding ECG leads I, aVF, and V1; no ECG abnormalities are present in the patient with moderate PAH, despite a chronically elevated RV pressure load. Third row panels: the ventricular gradient (VG) projections (QRSST interval) on the x-, y-, and z-axes, revealing that the VG projection on the x-axis gradually becomes smaller, proportionate to the degree of chronic RV pressure load. The relationship between the QRS integral, the T-wave integral, and the VG is illustrated in the bottom row for the VG projection on the x-axis (VGx) in the frontal plane. The VG (solid black line) is the vectorial sum of the QRS (dashed green line) and T (solid gray line) integrals. VGx is the projection of the VG on the x-axis (dashed black line). Of note is that all numbers in the bottom panels are expressed in mV·ms, with a scale of 0–75 mV·ms for the control subject with normal RV pressure load and a scale of 0–25 mV·ms for the patients with moderate and severe PAH.

### Table 1. PAH patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP, mmHg</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Mean PAP, mmHg</td>
<td>56</td>
<td>14</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
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<td>4</td>
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<tr>
<td>PVR, mmHg·1/1·min</td>
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<tr>
<td>Mixed venous SpO₂, %</td>
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<td>10</td>
</tr>
<tr>
<td>Cardiac index, 1·m²·min⁻¹</td>
<td>2.3</td>
<td>0.9</td>
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n = 72 (15 men). PAH, pulmonary arterial hypertension; RAP, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SpO₂, oxygen saturation in blood.

**Right heart catheterization.** All PAH patients underwent right heart catheterization, during which right atrial pressure, PAP, pulmonary capillary wedge pressure, and mixed venous oxygen saturation were measured. Cardiac output was calculated using Fick’s principle. Oxygen consumption was measured during right heart catheterization. Pulmonary vascular resistance (in mmHg x t) was calculated by dividing the transpulmonary gradient (pressure difference between mean PAP and pulmonary capillary wedge pressure) by cardiac output.

**ECG analysis.** Conventional 10-s ECGs were recorded by certified ECG technicians using the standard 12-lead electrode configuration with patients in supine position. ECGs were recorded on commercially available electrocardiographs (MAC VU and MAC 5000, GE Healthcare; and Megacart, Siemens), at a paper speed of 25 mm/s; sensitivity 1 mV = 10 mm; sample frequency of 500 Hz. All ECGs were assessed for the presence of conventional 12-lead ECG criteria of RV hypertrophy (27). ECGs were also analyzed with LEADS, our noncommercial, research-oriented ECG analysis program that automatically renders amplitudes, areas, and vector directions (10). In short, LEADS automatically selects beats for averaging based on signal quality criteria (baseline, noise). This selection of beats is then reviewed and edited by the investigator. The thus selected beats are then averaged by LEADS. After manually reviewing and editing the onset and end of the QRS complex, a synthesized vectorcardiogram is generated with the inverse Dower matrix (10, 12). Parameters derived from this vectorcardiogram, such as the VG magnitude (mV·ms) and spatial orientation (azimuth°, orientation in the transversal plane, and elevation°, deviation from the transverse plane), are then calculated. The VG is defined as: \( \int \hat{H}(t) \, dt \), in which \( \hat{H}(t) \) is the heart vector, as represented in the X, Y, and Z leads of the vectorcardiogram (5). This integral, taken over the QRSST interval, is nonzero due to action potential morphologic differences in the ventricles, most often thought of as APD differences (11). Orientation of the axes is in accordance with the American Heart Association recommendations: x-axis positive from right to left, y-axis positive in craniocaudal direction, and z-axis positive in anteroposterior direction (24). Control ECGs were selected from a large database of healthy students of the Leiden University Medical Faculty. All ECGs were scrutinized for normality according to the Minnesota criteria by an experienced cardiologist (4). Prior to the use of the selected ECGs for comparison in this study, all ECGs were anonymized. All ECGs were analyzed twice by the first author (I. R. Henkens), and a third time by the second author (K. T. B. Mouchaers) to determine the intraobserver and interobserver variability for calculating the VG. Because the VG depends on heart rate (38) and sex, but not on the pressure scale is set at 0 –100 mmHg in the patients with moderate and severe PAH. Of note is that the pressure scale is set on different levels of chronic right ventricular (RV) pressure load on the ECG and vectorcardiogram is illustrated in a patient without pulmonary arterial hypertension (PAH) (catheterized for exclusion of familial PAH after inconclusive transthoracic contrast echocardiography; left), a patient with moderate PAH (middle), and a patient with severe PAH (right), respectively. Top panels: RV and pulmonary artery (PA) pressures (PAP). Horizontal lines, mean PAP. Mean PAP = 11 mmHg in the patient with PAH. Mean PAP = 43 mmHg in the patient with moderate PAH, and mean PAP = 64 mmHg in the patient with severe PAH. Of note is that the pressure scale is set at 0–20 mmHg in the control subject with normal RV pressure load, whereas the pressure scale is set at 0–100 mmHg in the patients with moderate and severe PAH. Second row panels: corresponding ECG leads I, aVF, and V1; no ECG abnormalities are present in the patient with moderate PAH, despite a chronically elevated RV pressure load. Third row panels: the ventricular gradient (VG) projections (QRSST interval) on the x-, y-, and z-axes, revealing that the VG projection on the x-axis gradually becomes smaller, proportionate to the degree of chronic RV pressure load. The relationship between the QRS integral, the T-wave integral, and the VG is illustrated in the bottom row for the VG projection on the x-axis (VGx) in the frontal plane. The VG (solid black line) is the vectorial sum of the QRS (dashed green line) and T (solid gray line) integrals. VGx is the projection of the VG on the x-axis (dashed black line). Of note is that all numbers in the bottom panels are expressed in mV·ms, with a scale of 0–75 mV·ms for the control subject with normal RV pressure load and a scale of 0–25 mV·ms for the patients with moderate and severe PAH.

![Fig. 1. The effect of different levels of chronic right ventricular (RV) pressure load on the ECG and vectorcardiogram is illustrated in a patient without pulmonary arterial hypertension (PAH) (catheterized for exclusion of familial PAH after inconclusive transthoracic contrast echocardiography; left), a patient with moderate PAH (middle), and a patient with severe PAH (right), respectively. Top panels: RV and pulmonary artery (PA) pressures (PAP). Horizontal lines, mean PAP. Mean PAP = 11 mmHg in the patient with PAH. Mean PAP = 43 mmHg in the patient with moderate PAH, and mean PAP = 64 mmHg in the patient with severe PAH. Of note is that the pressure scale is set at 0–20 mmHg in the control subject with normal RV pressure load, whereas the pressure scale is set at 0–100 mmHg in the patients with moderate and severe PAH.](http://ajpheart.physiology.org/)
existing correlations between ROC curves derived from the same cases. Binary logistic regression analysis was used to determine the optimal model for classification of increased RV afterload for both ECG-derived variables and vectorcardiogram-derived variables. Subsequently, the optimal model was used in a bootstrapping analysis to determine the accuracy of the odds ratio (OR) in this classification model. Pearson correlation analysis was used for analysis of intraobserver and interobserver variability, as well as for comparison of the VG with CMR-derived variables of RV mass, and volume. A value of P < 0.05 was considered to be statistically significant.

RESULTS

Patient characteristics at the time of the diagnostic right heart catheterization are presented in Table 1. Controls (n = 144, 30 male) were younger than patients (mean age: 19.7 ± 1.3 yr vs. 43.7 ± 22.8 yr; P < 0.001). Mean heart rate was 82 ± 17 beats/min in PAH patients vs. 80 ± 14 beats/min in controls (P = 0.47). Calculation of the VG proved to be highly reproducible, with both excellent intraobserver (r = 0.994, P < 0.001) and interobserver agreement (r = 0.992, P < 0.001).

Typical examples of RV and PAPs with the corresponding ECG and vectorcardiogram findings are presented in Fig. 1 for a healthy subject (catheterized for exclusion of familial PAH after inconclusive trans thoracic contrast echocardiography), a patient with moderate PAH, and a patient with severe PAH. It can be appreciated from leads I and aVf that an intermediate frontal plane QRS axis is present in the subject without PAH as well as in the patient with moderate PAH, whereas a right axis deviation is present in the patient with severe PAH. Furthermore, lead V1 is within normal limits for both the subject without PAH and the patient with moderate PAH, whereas lead V1 qualifies for RV hypertrophy in the patient with severe PAH: R > S and R > 5 mm, initial P wave > 1 mm high and wide, and the T wave is discordant with the QRS, reflecting RV strain. A closer look at the projection of the VG on the x-, y-, and z-axes reveals that the VG projection on the x-axis (net QRS axis area in the X lead) becomes smaller proportional to the degree of chronic RV pressure load. The lower panels illustrate also that chronic RV pressure load leads to a proportionate decrease in QRS and T integral vectors and to an increase in QRS-T spatial angle (Table 2), together resulting in a smaller and differently oriented VG.

In general, conventional ECG criteria had low diagnostic accuracy for the presence of increased RV afterload (Table 3). With a sensitivity of 84% and a specificity of 96%, a QRS axis...
>90° in the frontal plane was the conventional ECG parameter with the highest individual diagnostic accuracy for chronically increased RV pressure load (Table 3). Multivariable binary logistic regression analysis performed in a backward stepwise fashion (removal if \( P > 0.10 \), inclusion if \( P < 0.05 \), a priori chance of PAH = 0.33) rendered the following formula for optimal prediction of presence of PAH: \( y = 2.204 \cdot (\text{presence of } rS'r \text{ or } rSR' \text{ in lead } V1) + 3.079 \cdot (\text{presence of } R:S > 1 \text{ in lead } V1 \text{ with } R > 0.5 \text{ mV}) + 4.542 \cdot (\text{presence of QRS axis} > 90°) - 6.679 \) (sensitivity = 89% and specificity = 94%; \( P < 0.001 \)). Receiver-operating-characteristic curves for diagnosis of increased RV pressure load are presented in Fig. 2. Although sensitivity and specificity did not differ importantly between the prediction based on a multivariable analysis compared with the single prediction of the presence of QRS axis > 90°, the multivariable prediction showed a larger AUC than QRS axis > 90° alone.

Significant differences in the VG were observed, however, between PAH patients and healthy controls. In general, in PAH patients the VG assumed a different orientation from healthy controls and was also considerably smaller: 34.8 ± 17.5 vs. 85.9 ± 27.6 mV·ms (\( P < 0.001 \); Fig. 3). It is easily appreciated from the bottom right panel that VG magnitude alone cannot accurately separate PAH patients and healthy controls. Multivariable analysis showed that a combination of VG magnitude and orientation had superior discriminating power to either variable alone, especially the VG projection on the x-axis. Multivariable analysis in a stepwise forward fashion (inclusion if \( P < 0.01 \), removal if \( P > 0.05 \)), including the respective orthogonal projections of the mean QRS integrals, mean T-wave integrals, and the mean VGs, illustrated that of all the significantly related single variables, the VG projection on the x-axis was the variable with the highest discriminating power (Table 2). PAH patients and controls were therefore compared for the VG projection on the x-axis. The VG magnitude projection on the x-axis (AUC = 0.993) had a significantly larger AUC than presence of a QRS axis > 90° (dichotomous variable; AUC = 0.900, z-score = 3.36, \( P < 0.01 \)), QRS axis in the frontal plane (continuous variable; AUC = 0.904, z-score = 2.89, \( P < 0.01 \)), and the composite model of conventional ECG parameters (AUC = 0.945, z-score = 2.27, \( P < 0.05 \); see Fig. 2). Binary logistic regression analysis rendered the following formula for prediction of the presence of increased RV pressure load by the x component of the VG: \( y = -0.195 \cdot V_{Gx} + 6.195 \) (OR = 0.82 for each unit increase in VG projection on the x-axis) with a sensitivity of 97% and a specificity of 94%. Bootstrapping analysis validated the adequacy of this model, rendering a 95% confidence interval for the OR of 0.74–0.91 (\( P < 0.001 \)) based on a normal distribution of the regression coefficients over the bootstrap samples. To assess whether the VG projection on the x-axis could differentiate between mild-to-moderate and severe PAH, patients were stratified in two categories according to mean PAP level: mean PAP = 25–45 mmHg (\( n = 16 \)) and mean PAP > 45 mmHg (\( n = 56 \)). Figure 4 illustrates that the VG projection on the x-axis was already markedly decreased in patients with mildly to moderately increased RV pressure load (mean PAP = 25–45 mmHg), and even more in patients with a severely increased RV pressure load (mean PAP > 45 mmHg). One-way analysis of variance showed that PAH patients with a mean PAP = 25–45 mmHg had a VG projection on the x-axis that was significantly lower than in controls (17.5 ± 15.0 mV·ms vs. 68.1 ± 22.0 mV·ms, \( P < 0.001 \)), but still higher than in PAH patients with a mean PAP > 45 mmHg (17.5 ± 15.0 mV·ms vs. 2.8 ± 16.1 mV·ms; \( P = 0.033 \)). Here, too, the projection of the VG on the x-axis showed the highest discriminating power, since the VG magnitude alone did not differentiate between patients with a mean PAP = 25–45 mmHg and patients with a mean PAP > 45 mmHg, although VG magnitude in both groups of PAH patients was lower than in controls (Table 2). Since the VG is the vectorial sum of the QRS and T integrals, projections of QRS and T integrals as well as the QRS-T spatial angle were also calculated. Mean QRS integral and mean T-wave integral magnitudes and projections on the x-, y-, and z-axes were generally different between controls and PAH patients, although the distinction between mild-to-moderate PAH and severe PAH could only be made by QRS integral projections on the x- and z-axes, the T-wave integral projection on the z-axis, and again the VG projection on the x-axis (Table 2). Overall, the QRS-T spatial angle was higher in patients with a chronically increased RV afterload than controls, signifying a higher degree of discordance between depolarization and repolarization (Table 2).

CMR showed that RV mass was related to the VG projection on the x-axis (Fig. 5A), and a trend was observed toward a relation between a higher RV volume and a smaller VG projection on the x-axis (Fig. 5B).

**DISCUSSION**

The key finding of the present study is that it proves that the ECG-derived VG is highly accurate in detecting chronic increase in RV pressure load, and as such it can be used to distinguish...
between normal RV pressure load, mildly to moderately increased RV pressure load, and severely increased chronic RV pressure load. Furthermore, the ECG-derived VG proved to be of higher diagnostic accuracy for chronically increased RV pressure load than conventional ECG parameters. Available CMR data suggest that VG changes in PAH patients reflect changes in APD heterogeneity related to RV remodeling as a result of an increased RV pressure load.

Vectorcardiography vs. electrocardiography. The general approach toward ECG interpretation is one directed at individu
our study support this view, yet underline the importance of clinical use or screening purposes (2, 26, 29, 32). The results of the HG studies demonstrated that the calculation is not sufficient for diagnostic potential of conventional 12-lead ECG parameters used to diagnose RV hypertrophy in newborns and patients with an increased RV afterload, the vectorcardiogram (VG) requires only straightforward integration over the QRST complex of the instantaneous heart vector (that can be synthesized from the ECG leads by a simple matrix multiplication) (12), this algorithm can easily be implemented in existing ECG analysis software, as we did in our LEADS program.

Despite the recognition of certain ECG characteristics in newborns and patients with an increased RV afterload, the diagnostic potential of conventional 12-lead ECG parameters for increased RV afterload has been reported as insufficient for clinical use or screening purposes (2, 26, 29, 32). The results of our study support this view, yet underline the importance of using the full potential of an electrocardiogram. Contemporary software now renders (synthesized) vectorcardiogram-derived calculations with such ease that clinical application of this information is certainly feasible (10).

Rationale for using the VG. The VG is oriented toward the left and slightly anteroinferior in healthy persons (Fig. 3) within a smaller range than the mean QRS axis orientation in the frontal plane (38). The VG is the integrated ventricular APD heterogeneity, which is the 3-D sum of the integrated ventricular depolarization and repolarization heterogeneities (11). As such, the VG has a strong physiological link to the way in which the ventricular APD distribution is affected by chronic RV pressure load. Any intraindividual change in the VG magnitude and orientation signifies an alteration in APD heterogeneity in the ventricles, and hence a change in myocardiad electrophysiological properties (11, 19). Chou et al. (8) evaluated the use of QRS loop area for diagnosis of RV hypertrophy. As discussed by the authors, the QRS loop area is the sum of all depolarization vectors, allowing appreciation of the resultant spatial orientation and the ratio of leftward and rightward oriented forces, rendering evaluation of quantitative conventional ECG parameters of RV hypertrophy superfluous (8). Cowdery et al. (9) recognized the importance of the QRS loop area, and they further improved diagnostic accuracy for RV hypertrophy by interpreting QRS amplitude in the transversal plane (60% sensitivity and 96% specificity). Kawaguchi (20) further concluded that repolarization characteristics should not be overlooked, since in his diagnostic model for RV hypertrophy, the combined T loop area and direction rendered the best result. The high diagnostic accuracy for the presence of chronic RV pressure load of the 3D V-G (Fig. 3), which is the sum of QRS and T integrals, is in accordance with these reports regarding changes in QRS complex and T-wave morphology in patients with an increased RV pressure load (8, 9, 20).

There is a distinct evolution of ECG characteristics with developing PAH (17). Changes in VG with increasing RV pressure load are best assessed in 3-D, although single-lead assessment is theoretically possible (18, 19). Much as we observed in rats (17), a higher RV pressure load effectively cancels out the net LV contribution to the VG (Fig. 1, bottom panel) (1, 6, 17). Obviously, this cancellation effect occurs because RV pressure load-induced RV hypertrophy introduces an additional vectorial force over the LV contribution to the VG. In healthy controls (assumed mean PAP < 25 mmHg, n = 144), the VG projection on the x-axis is much larger than in patients with a chronically increased RV pressure load (mean PAP > 25 mmHg, n = 72). Furthermore, the VG projection on the x-axis allows distinction between a mildly to moderately elevated RV pressure load (mean PAP = 25–45 mmHg) and a severely elevated RV pressure load (mean PAP > 45 mmHg, n = 56).

Fig. 4. In healthy controls (assumed mean PAP < 25 mmHg, n = 144), the VG projection on the x-axis is much larger than in patients with a chronically increased RV pressure load (mean PAP > 25 mmHg, n = 72). Furthermore, the VG projection on the x-axis allows distinction between a mildly to moderately elevated RV pressure load (mean PAP = 25–45 mmHg) and a severely elevated RV pressure load (mean PAP > 45 mmHg, n = 56).

A

B

Fig. 5. RV mass showed an inverse relation with the VG projection on the x-axis (r = −0.323, P = 0.048) (A), and there was a trend toward a similar inverse relation between a higher RV end-diastolic volume and the VG projection on the x-axis (r = −0.308, P = 0.067) (B). RVEDVI, RV end-diastolic volume indexed for body surface area; LVEDVI, left ventricular end-diastolic volume indexed for body surface area.
APD heterogeneity substantially opposing the net LV APD heterogeneity. Thus, mild-to-moderate elevation of RV pressure load decreases VG magnitude, whereas VG orientation is largely maintained (Table 2 and Fig. 4). Further elevation of RV pressure load does not necessarily lead to a further decrease of VG magnitude, although it may drastically affect VG orientation (Figs. 1 and 4 and Table 2) (11). A comparison with CMR studies in a subgroup of patients showed that RV pressure load-induced changes in APD heterogeneity were related to changes in RV-to-LV mass ratio rather than to changes in RV-to-LV volume ratio. In steadily developing PAH, hypertrophy occurs already with mildly elevated PAP, before dilatation of the RV is seen. (17, 36). This may explain the closer association of the VG projection on the x-axis with RV hypertrophy rather than with RV dilatation.

Limitations. In the absence of available ECGs from the time before development of PAH, we compared the ECGs of patients with a mildly to moderately elevated RV afterload as well as the ECGs of patients with a severely elevated RV afterload with the ECGs of healthy control subjects. Since we may assume that idiopathic PAH patients once had a normal RV afterload, comparison with ECGs from healthy individuals seems to be the most obvious alternative (30, 33). This cross-sectional approach allows appreciation of the supposed evolution of changes in the VG in response to an increasing RV pressure load. The selection of patients with idiopathic PAH precludes application of our findings to patients with important lung disease or left-sided heart disease. However, since even a mildly to moderately elevated RV pressure load was associated with marked differences in the VG, the ECG seems a suitable screening tool for increased RV pressure load in selected groups of patients, such as relatives of patients with familial PAH, patients with HIV, systemic sclerosis, portal hypertension, or other diseases associated with development of PAH (2, 26). Despite the obvious advantages of simply projecting the VG in the direction of interest (the x-axis), a potential downside of this approach is the observed nonlinear relation between PAH severity and the degree of chronic RV pressure load (Fig. 4), which precludes classification of chronic RV pressure load beyond the categories of normal, mild-to-moderate, and severe RV pressure load. The size of our study group did not permit use of a learning set and test set. However, bootstrapping analysis confirmed the validity of the proposed predictive model of increased RV pressure load. The uneven sample sizes of mild-to-moderate PAH patients and severe PAH groups is suboptimal, yet a representative reflection of the high number of PAH patients with a mean PAP > 45 mmHg at the time of diagnosis. The limited sample size of patients with mild-to-moderate PAH in our study may have affected the ability of the other ECG variables to discriminate between mild-to-moderate PAH and severe PAH.

Clinical implications. In patients with a genetic profile or disease known to predispose to PAH, serial ECG recording may prove a feasible concept for early detection of an increasing RV afterload. Apart from incorporation of calculations based on the VG into software for electrocardiographs, another way of indirectly assessing the presence of chronic RV pressure load may be to calculate QRST areas in a lead with a lead vector that assumes about the direction of the x-axis, such as lead I or V6. Whether such an individual lead-based VG approximation will prove to be of similar diagnostic accuracy deserves further study. Screening for PAH among patients at risk is still subject to debate, but it is generally regarded as very costly because of the high rate of false negative diagnoses with the available tools for noninvasive detection (28, 37). The improved ECG detection of RV pressure load using the VG may dramatically cut the cost of screening. Whether sequential ECG recording allows for early distinction of “responders” from “nonresponders” to PAH-attenuating therapy by detection of VG changes, a distinction currently made by repetitive 6-min walking tests, cardiac magnetic resonance imaging or right heart catheterization deserves further study (21, 35). In patients without congenital or acquired left-sided heart disease and/or pulmonary disease, the VG may prove to be an important tool for screening purposes and follow-up.

In conclusion, chronically increased right ventricular pressure load induces changes in ventricular APD heterogeneity, which are reflected by distinct changes in the ventricular gradient. The ECG-derived ventricular gradient can be used with high accuracy for detection of chronically increased right ventricular pressure load, and it is a potentially useful tool for follow-up in selected groups of patients. VG changes in PAH patients likely reflect changes in ventricular APD heterogeneity related to RV remodeling as a result of an increased RV pressure load.

DISCLOSURES
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REFERENCES


