Electrocardiographic Detection and Monitoring of Pulmonary Hypertension

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Abstract

Initial symptoms of pulmonary hypertension (PH) are easily missed, while early diagnosis and treatment is essential. Pulmonary arterial pressure (PAP) assessment by right heart catheterization or echocardiography is not feasible for periodic monitoring of patients at risk of developing PH. Here we investigate the possible use of the electrocardiogram (ECG) as a screening instrument for early PH detection and for monitoring its course.

We studied patients in whom at two different dates mean PAP measurements were done (either by echocardiography or by right heart catheterization) and in whom two 12-lead ECGs had been made within three months from the dates on which the mean PAP assessments were done. In each of these patients, the change in mean PAP was classified into one of three categories: decrease > 7.5 mmHg, increase > 7.5 mmHg, or limited change (increase/decrease ≤ 7.5 mmHg). The ECG output variable was a projection of the ventricular gradient (VG) optimized for right ventricular pressure overload detection: VG_{rvpo}.

A total of 39 patients (15/24 male/female, age 60±12 years) was studied. Mean PAP and VG_{rvpo} changed by −15±7 mmHg and −13±26 mV·ms in the mean PAP decrease group, and by 12±4 mmHg and 8±12 mV·ms in the mean PAP increase group, respectively. The VG_{rvpo} changes in the mean PAP increase and decrease groups differed significantly ($P<0.05$).

These results suggest that the ECG can be used as a monitoring instrument to detect changes in PAP.

1. Introduction

Pulmonary hypertension (PH) has several distinct causes[1]. The general characteristic in all PH variants is right ventricular (RV) pressure overload and, hence, increased RV wall tension. When this condition sustains, RV hypertrophy and dilatation may develop[2]. PH has an unfavorable prognosis: estimated survival at three years after the initial diagnosis of PH is 55%[3].

Often, initial PH diagnosis is delayed, partly due to often mild and nonspecific symptoms and absence of overt signs of RV dysfunction in the early stage of the disease. Early detection and treatment of PH is essential in order to improve prognosis[4-6]. Especially in pulmonary arterial hypertension (PAH) and chronic thromboembolic PH, improvement of prognosis can be achieved by timely use of dedicated medication or surgery. Hence, subjects at risk for the development of PH, such as patients with connective tissue disease, portal hypertension, or patients with a history of pulmonary embolism, should preferably periodically be monitored.

Gold standard for the diagnosis of PH is the angiographically measured mean pulmonary arterial pressure (PAP). Usually, mean PAP >25 mmHg is considered as PH[7]. Given the costs, risks and burden of this invasive catheterization procedure, echocardiographic mean PAP assessment is usually preferred as a slightly less precise, but non-invasive alternative. However, this specialized form of echocardiography is logistically and financially not suited for screening purposes in populations with an increased risk of developing PH.

Our group investigates if the (widely available low cost low burden) electrocardiogram (ECG) can be used as a screening instrument for early PH detection and for monitoring its course. Traditional 12-lead ECG diagnosis has limited value for PH detection: sensitivity is 55% and specificity is 70%[8], possibly because the ECG criteria aim to detect RV hypertrophy (that may not yet have developed). Recently, we showed that the ventricular gradient (VG), computed in a vectorcardiogram (VCG) that is mathematically synthesized from the 12-lead ECG, is associated with mean PAP[9]. In a transversal study, we demonstrated a significant correlation between a VG projection optimized for RV pressure overload (VG_{rvpo}) and the angiographically measured mean PAP. The current study involves a longitudinal approach in the same patient group, and aims to associate intra-individual changes in VG_{rvpo} with intra-individual mean PAP changes. Thus, it may be possible to predict changes in mean PAP by measuring changes in the ECG, notably by measuring changes in VG_{rvpo}.

2. Methods

For our here described investigation we selected patients from a group that was previously transversally studied[9]. That study group consisted of 63 subjects who had been evaluated for suspected PH by right heart catheterization. All patients were screened according to the institutional protocol based on the current guidelines[7]. Prior to right heart catheterization, a conventional 10-second 12-lead ECG was made and 2-dimensional transthoracic echocardiography was performed. The underlying etiology of PH was determined according to the Dana Point classification[7]. All data were prospectively collected in the departmental Cardiology Information System (EPD Vision®, Leiden University Medical Center, the Netherlands) and were retrospectively analyzed. Patients were included if an ECG was available within 40 days of the right heart catheterization. Exclusion criteria were: atrial fibrillation, pacemaker rhythm, prior myocardial infarction and complex congenital heart disease. Additionally, to reduce the possibility that abnormal electrical activity of the left ventricle (LV) would influence the ECG, patients with increased LV mass index (>95 g/m^2 and >115 g/m^2 for female and male patients, respectively) or increased relative wall thickness (>0.42), measured by echocardiography, were excluded[10].

For our current study, we checked in all patients of the above-mentioned transversally studied group[9] if a second mean PAP value (assessed by echocardiography or measured by catheterization) was available, either preceding or following the index catheterization, in combination with a second 12-lead ECG made within 3 months from the date on which the second mean PAP value was determined. Because ECGs, echocardiograms and catheterizations were made/performed in the course of regular clinical care, certain measurements needed for the determination of mean PAP were sometimes not indicated; these patients were excluded from the current study.

Mean PAP was determined as follows. When a second cardiac catheterization had been performed and mean PAP was not directly reported, it was assessed by adding 2/3 of the diastolic PAP to 1/3 of the systolic PAP. When a second echocardiogram was made, systolic PAP was assumed to be equal to RV systolic pressure (patients with RV outflow obstruction were excluded); RV systolic pressure was estimated by adding the tricuspid regurgitant pressure gradient and the estimated right atrial pressure (taken 5 mmHg when the vena cava collapsed during the respiratory cycle, or 10 or 15 mmHg, depending on the – non-collapsing – vena cava behavior). Then, mean PAP was computed as 0.61· systolic PAP + 2[8].

Finally, patients who had two valid mean PAP assessments, each in combination with a nearby ECG, were evaluated as follows. In each of these patients, the change in mean PAP was classified into one of three categories: decrease > 7.5 mmHg, increase > 7.5 mmHg, or limited change (decrease/increase ≤ 7.5 mmHg). Then, the differences in VG_{rvpo} in the mean PAP decrease and increase groups were statistically evaluated by an unpaired t-test.

3. Results

A total of 39 patients (15/24 male/female, age 60±12 years) had sufficient data to be included. Table 1 and Figure 1 give a numerical and pictorial representation of the mean±SD changes in mean PAP and VG_{rvpo} in these patients.

Table 1. Changes in mean PAP (ΔmeanPAP) and in VG_{rvpo} (ΔVG_{rvpo}) in 39 patients. PAP = pulmonary arterial pressure, VG = ventricular gradient, rvpo = right ventricular pressure overload, * = statistically significantly different from the "Decrease > 7.5 mmHg" group (P<0.05).

Category	N	ΔmeanPAP (mmHg)	ΔVG_{rvpo} (mV·ms)
Decrease > 7.5 mmHg	9	−15±7	-13±26
Limited change	19	0±4	1±15
Increase > 7.5 mmHg	11	12±4	8±12*
Total	39	1±14	0±19

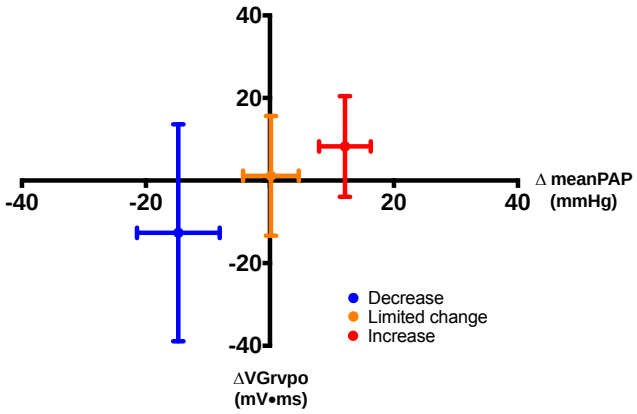

Figure 1. Changes in mean PAP (ΔmeanPAP) and in VG_{rvpo} (ΔVG_{rvpo}) in the study group. PAP = pulmonary arterial pressure, VG = ventricular gradient, rvpo = right ventricular pressure overload. Error bars represent the standard deviations.

4. Discussion

Our study demonstrates that an increase/decrease in RV pressure is associated with an increase/decrease in VG_{rvpo}. This implies that the ECG can potentially be used as an instrument to monitor RV pressure.

Serial analysis is an often used strategy to deal with biological variability: it is usually applied to detect trends within subjects when the physiological variable of interest has substantial inter-individual dispersion. This is the case for VG. *E.g.,* the average magnitude of the VG vector in female normal subjects is 81 mV·ms with a standard deviation of 23 mV·ms and 2nd and 98th percentile values of 39 and 143 mV·ms; the average magnitude of the VG vector in male normal subjects is 110 mV·ms with a standard deviation of 29 mV·ms and 2nd and 98th percentile values of 59 and 187 mV·ms[11]. Trend detection is essential in monitoring, and an ECG variable that is sensitive for mean PAP changes would be of substantial clinical interest. When there is no RV outflow obstruction, changes in PAP parallel changes in RV pressure. Changes in RV pressure alter the action potentials of the involved ventricular myocytes by mechano-electrical feedback[12]. This implies that PAP and RV pressure changes give instantaneously rise to ECG changes and, consequently, changes in the VG, best reflected in the RV-pressure-overload-optimized VG projection, VG_{rvpo}.

An example of ECG changes associated with RV pressure changes is shown in Figure 2. Both ECGs are not pathological, but the patient had PH when the initial ECG was made while there was no PH when the second ECG was made. In this example patient, the pulmonary artery pressures were both measured by catheterization (gold standard). This patient follows the typical behaviour as seen in our study group (see Table 1 and Figure 1): an increase/decrease in RV pressure is associated with an increase/decrease in VG_{rvpo}.

As our study was retrospective and had to rely on clinically obtained measurements that were not specifically done for research purposes, we cannot produce a fair estimate of the accuracy of the ECG as an instrument to monitor RV pressure changes. It is generally known that echocardiographic assessment of RV pressure has limited accuracy. Despite the strong correlation of the tricuspid regurgitation velocity and tricuspid regurgitation pressure gradient, Doppler-derived pressure estimation may be inaccurate in the individual patient[8]. Our study is hampered by the fact that most of our data rest on the comparison of one catheterization-based and one echocardiography-based mean RV pressure assessment. Also, because ECGs were not routinely made together with the echocardiograms, we had to tolerate a rather large difference in time between the echocardiogram and the corresponding ECG, weakening their degree of association. We have handled the above-mentioned error sources by introducing the "Limited change" category, in addition to the "Mean PAP increase" and "Mean PAP decrease" categories. Notwithstanding the accuracy limitations, our results suggest that relevant changes in RV pressure can be detected by serial ECG analysis.

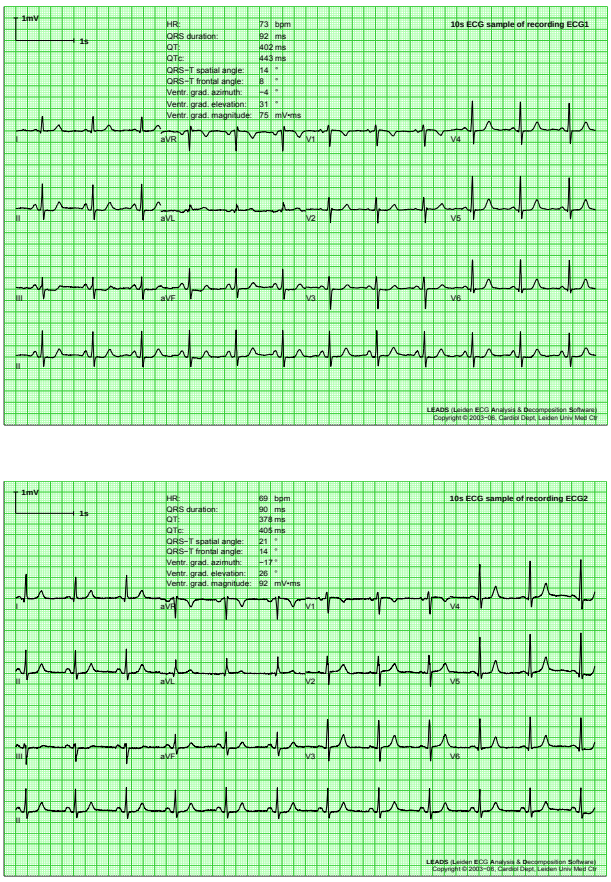

Figure 2. Example ECGs of one patient (female, 54y when the first ECG was made), made 23 months apart. Corresponding mean PAP and VG_{rvpo} were 33 mmHg and −36 mV·ms (upper panel, initial ECG), and 23 mmHg and −55 mV·ms (lower panel, second ECG), respectively. Pressures were measured by catheterization.

5. Conclusions

Our study demonstrates, for the first time, that serial ECG analysis, notably analysis of the dynamics in VG_{rvpo}, has potential use for monitoring patients at risk for developing PH or for monitoring patients treated for PH. Such ECG-based monitoring could be specifically useful in those PH patient categories for which effective treatment is available, *e.g.*, in patients with PAH, chronic thromboembolic PH, connective tissue disease and portal hypertension. To assess the accuracy/reliability of this ECG-based monitoring method, validation with accurate RV pressure data, obtained by cardiac catheterization, is needed. We are currently working on a database of comparable pathology as the here described study group, but with two right-heart catheterizations in every patient.

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