The right ventricle under acute and chronic overload: early detection of right ventricular dysfunction
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ECG DETERMINANTS IN ADULT PATIENTS WITH CHRONIC RIGHT VENTRICULAR PRESSURE OVERLOAD DUE TO CONGENITAL HEART DISEASE: RELATION WITH PLASMA NEUROHORMONES AND MRI PARAMETERS

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Objective: The clinical significance of electrocardiographic (ECG) parameters and other non-invasive quantitative parameters for right ventricular (RV) function in patients with chronic RV pressure overload due to congenital heart disease is not yet established. In this study we retrospectively examined the changes of ECG parameters over time and their correlation with other quantitative RV function parameters.

Methods: Forty-eight patients with chronic RV pressure overload due to the following congenital heart diseases were included: 9 congenitally corrected (cc) transposition of the great arteries (TGA), 12 surgically corrected TGA, and 27 patients with a subpulmonary pressure overloaded RV. QRS duration and dispersion were measured manually from standard ECG, registered twice within an interval of 5 years. RV end diastolic volume (EDV) and RV mass were determined by magnetic resonance imaging (MRI). Brain natriuretic peptide (BNP) plasma levels were measured.

Results: QRS duration and QRS dispersion increased in all patient groups during the follow-up period. QRS duration increased significantly in ccTGA (p=0.04) and in the subpulmonary pressure overloaded RV group (p=0.01). QRS dispersion increased significantly in patients with surgically corrected TGA (p=0.03) and in the subpulmonary pressure overloaded RV group (p=0.02). A significant correlation was found between QRS duration and RVEDV (r=0.71; p<0.0001). RV mass was significantly correlated with QRS duration in patients with tetralogy of Fallot (TOF) (r=0.67; p<0.01). Mean plasma BNP levels (6.6 (5.4) pmol/L) were increased compared to normal reference values, but no correlation was found with ECG parameters or RV systolic pressure. No malignant arrhythmia or sudden death occurred.

Conclusions: Our study showed a gradual worsening of ECG parameters in asymptomatic or minimally symptomatic patients with chronic RV pressure overload, regardless of the nature of congenital heart disease. In all patients, a significant positive correlation was found between QRS duration and RVEDV, and in TOF patients, also between QRS duration and mass.
INTRODUCTION

Ventricular arrhythmia is an important cause of death in patients with a chronic pressure overloaded right ventricle (RV) due to congenital heart disease. Stratification of patients at risk of life threatening arrhythmias is therefore mandatory in clinical follow-up, ideally by means of sensitive and specific predictive indices, which are easy to obtain in a non-invasive way. Several studies have shown that duration of the QRS complex more than 180 ms, and increased QRS dispersion on the surface electrocardiography (ECG) are associated with an increased risk of malignant ventricular dysrhythmias in patients with tetralogy of Fallot. RV failure is another important cause of death in patients with chronic RV pressure overload. Only few quantitative parameters for RV function are available. Novel techniques of volumetry such as magnetic resonance imaging (MRI) which may overcome the limitations of other imaging techniques for the assessment of the RV volumes and mass have become available.

Other quantitative parameters such as plasma neurohormones are gaining an important role in the early diagnosis of heart failure. Few studies have investigated the correlation between RV function and brain natriuretic peptide (BNP) levels, although recent literature has shown that plasma concentrations of BNP are highly accurate for prediction and detection of LV failure.

The aim of this study was to examine the clinical significance of ECG parameters, and the correlation with other non-invasive quantitative RV parameters, in adult patients with chronic RV pressure overload due to congenital heart disease.

METHODS

PATIENT POPULATION

Forty-eight patients with chronic RV pressure overload due to congenital heart disease in a tertiary referral center were examined in a retrospective study. The main inclusion criterion was chronic RV pressure overload (RVSP > 35 mm/Hg assessed by echocardiography) due to congenital heart disease without important additional hemodynamic lesions, in asymptomatic or minimally symptomatic patients (NYHA I or II). Patients were classified into 3 groups according to the nature of the congenital disease. Group 1 included 9 patients with congenitally corrected transposition (cc) of the great arteries (TGA). Group 2 consisted of 12 patients with surgically corrected TGA according to the Mustard or Senning procedures. Twenty-seven patients with a subpulmonary pressure overloaded RV were included in group 3. Group 3 was divided into 2 subgroups: a) 13 patients with tetralogy of Fallot (10 of these patients showed significant pulmonary regurgitation ranging between 30-50 ml per stroke and three patients less than 10 ml per stroke) and b) 14 patients with RV pressure overload due to other congenital heart disease (see table 1). The latter group consisted of 9 patients with residual pulmonary valve stenosis after valvulotomy, 4 patients with peripheral pulmonary stenosis, and 1 patient with primary pulmonary hypertension. Patients with irregular rhythm or pacemakers were not included in the study due to MRI technical features: irregular heart rate has a negative effect on the quality of MRI causing blurred images, pacemakers and leads can be damaged by the magnetic field, or cause internal burns due to the magnetic induction. The institutional Ethics Committee approved the study design and informed consent was obtained from all study subjects. Patient population and clinical characteristics are shown in table 1.
Table 1

<table>
<thead>
<tr>
<th>Clinical Characteristics of the Study Population</th>
<th>ccTGA</th>
<th>TGA</th>
<th>subpulmonary pressure overloaded RV</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>12</td>
<td>27</td>
</tr>
<tr>
<td>age, year</td>
<td>25.9 (6.1)</td>
<td>22.8 (3.4)</td>
<td>28.3 (8.7)</td>
</tr>
<tr>
<td>RVSP mmHg</td>
<td>113.9 (110-125)</td>
<td>114.4 (90-134)</td>
<td>56.1 (35-100)</td>
</tr>
<tr>
<td>NYHA class I/II</td>
<td>5/4</td>
<td>3/9</td>
<td>21/6</td>
</tr>
<tr>
<td>SVT/ no SVT</td>
<td>1/8</td>
<td>1/11</td>
<td>5/27</td>
</tr>
<tr>
<td>VT/ no VT</td>
<td>2/7</td>
<td>0/12</td>
<td>2/27</td>
</tr>
</tbody>
</table>

Values are mean (SD); ccTGA, congenitally corrected Transposition of the Great Arteries; NYHA, New York Heart Association; RVSP, right ventricular systolic pressure; TGA, surgically corrected Transposition of the Great Arteries; TOF, Tetralogy of Fallot.

* 9 patients with residual pulmonary valve stenosis, 4 with peripheral pulmonary stenosis, 1 with primary pulmonary hypertension.

**ELECTROCARDIOGRAPHY**

A standard (speed, 25 mm/s and 1 mV/cm standardization) resting 12 lead ECG registration was obtained during the last patient's visit at the outpatient clinic and compared with ECG registrations from a previous visit 5 years ago.

The ECG markers measured and analyzed included QRS duration and its interlead dispersion marker (QRSd). QRS duration was measured manually by one blinded observer and was defined as the maximal QRS length in any lead from the first inflection, to the final sharp vector crossing the isoelectric line. QRS dispersion was defined as the difference between the maximum and minimum QRS interval occurring in any of the 12 leads.

**MAGNETIC RESONANCE IMAGING**

MRI study was performed at the end of the 5 year follow-up. Study subjects were placed supine in a 1.5 Tesla MRI scanner with high power gradients (Vision, Siemens, Erlangen Germany). MRI acquisition involved a standardized protocol. Imaging sessions were initiated with scout images to determine the position of the heart in the thoracic cavity. Based on these images, an ECG triggered T1-weighted turbo spin echo series of axial images was acquired. A gradient-echo cine sequence was then performed in a plane bisecting the mitral valve orifice, and passing through the apex, visualizing the long-axis view in order to localize the atrioventricular valve plane. An ECG-triggered, ultrafast, breath-hold gradient-echo cine sequence with the following parameters: repetition time (TR) = R-R interval, time of echo (TE) = 4.8ms, slice thickness 10mm, imaging matrix = 256x256, field of view = 350mm, flip angle = 20°, was then used to acquire images in the short axis plane, in contiguous 10mm slices encompassing the heart from the valve plane to the apex. End-systolic and end-diastolic volumes were calculated from this multislice, multiphase image set.

**IMAGE ANALYSIS**

A Unix workstation was used for analysis of the MR images. MASS® (Medis, Leiden, The Netherlands) image analysis software was used to display multislice, multiphase images individually, and in a movie loop mode. End-diastolic (maximal ventricular volume) (EDV) frames were determined by manual outlining of a mid-ventricular slice in all phases. On end-
diastolic time frames, endocardial borders of the RV were outlined manually. Papillary muscles and the moderator band were not included in the ventricular volume. The enclosed RV cross-sectional areas were measured by computer, multiplied by section thickness, and summed up according to Simpson’s rule to provide RV volumes. Total MRI examination time was approximately 45 minutes.

**Brain Natriuretic Peptide**

Blood samples were obtained from the antecubital vein of all subjects after they had rested for at least 15 minutes. Blood was collected into chilled tubes containing EDTA and aprotinin (1.9 mg and 100 kIU/ml blood, respectively). The blood samples were promptly centrifuged (3000 rotations/minute for 10 minutes) and stored at minus 70°C until final analysis. BNP concentrations were determined with immunoradiometric assay kits (Shionoria, Osaka, Japan). Details of our methods have been published previously.

**Rhythm Measurements**

Twenty-four hour Holter recordings were analyzed by an experienced cardiac technician. The number and duration of the occurrence of supraventricular (SVT) and ventricular tachycardias (VT) were recorded and counted.

**Statistical Analysis**

Group data are expressed as mean ± SD. Student’s t tests were used to compare normally distributed variables. The relation between 2 factors was ascertained by plotting them against each other, and obtaining a linear regression line. The co-efficient of correlation (r) was obtained from the slope of this line. P≤0.05 was considered statistically significant.

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**Figure 1.** Changes in ECG markers during follow-up in patients with chronic RV pressure overload. ccTGA, congenitally corrected transposition of the great arteries; TOF, tetralogy of Fallot; TGA, surgically corrected transposition of the great arteries; rest: 9 patients with residual pulmonary valve stenosis, 4 with peripheral pulmonary stenosis, 1 with primary pulmonary hypertension. subpulmonary: all patients with TOF and all patients of the rest group. A) changes in QRS duration, B) changes in QRS dispersion.
RESULTS

By definition, the follow-up period was 5 years. There were no significant differences in age or sex between the studied patient groups. Holter recording in 7 patients showed SVT lasting less than 3 seconds (1 patient with ccTGA patient (6 SVTs), 1 with TGA (1) and 5 with subpulmonary pressure, 3 of them with tetralogy of Fallot (2,2,34) 2 of the subpulmonary rest group (both 1 SVT)). Four patients showed non-sustained VT lasting less than 3 seconds (2 ccTGA patients (1, 2 VTs respectively) and 2 subpulmonary pressure overloaded RV patients, both of the rest group (1,2)) (table 1). Six patients had QRS duration >180 ms (1 patient with ccTGA, 1 patient with TOF and 4 patients of the subpulmonary rest group). One patient with QRS>180 ms showed VT, while 5 patients with QRS>180 ms showed no VT. No malignant arrhythmia, or sudden death has occurred during the study interval.

Figure 2. Correlation between ECG markers and right ventricular (RV) end diastolic volume EDV in patients with chronic RV pressure overload. ccTGA, congenitally corrected transposition of the great arteries; TOF, tetralogy of Fallot; TGA, surgically corrected transposition of the great arteries; rest: 9 patients with residual pulmonary valve stenosis, 4 with peripheral pulmonary stenosis, 1 with primary pulmonary hypertension.

Subpulmonary: all patients with TOF and all patients of the rest group; total, all patients groups together.

ECG MARKERS

Mean QRS duration and QRS dispersion increased over time in all patient groups (Figure 1). We examined the occurrence of significant changes within the follow-up period in duration of QRS intervals, or QRS dispersion. Each group showed an increase of QRS duration and QRS dispersion during the five years. Significant increases in QRS duration during the follow-up period were found in the ccTGA group (0.107 (0.033) to 0.116 (0.039) ms; p=0.04), and in the subpulmonary pressure overloaded RV group (0.139 (0.036) to 0.130 (0.036) ms; p=0.01). (Figure 1a) Increase in QRS dispersion was significant in patients with TGA (0.098 (0.017) to 0.103 (0.014) ms; p=0.03), and in the subpulmonary pressure overloaded RV group (0.032 (0.014) to 0.043 (0.018) ms; p=0.02 (Figure 1b).
**Table 2.** Values are mean (SD); BNP, brain natriuretic peptide; EDV, end diastolic volume; ccTGA, congenitally corrected transposition of the great arteries, RV, right ventricle; TGA, transposition of the great arteries. *: 9 patients with residual pulmonary valve stenosis, 4 with peripheral pulmonary stenosis, 1 with primary pulmonary hypertension. #: Geigy Scientific Tables; Vol. 5 1990; #: Tulevski et al. Heart 2001:86:27-30

**RIGHT VENTRICULAR END DIASTOLIC VOLUME AND MASS**

RVEDV and RV mass parameters are summarized in table 2. Taken all groups together, there was a significant correlation between QRS duration and RVEDV ($r=0.76$; $p=0.0001$, Figure 2a). Taken the groups separately, we found a significant correlation in the group of patients with tetralogy of Fallot ($r=0.80$; $p=0.0009$, Figure 2), and in the subpulmonary rest group ($r=0.85$; $p<0.0001$, Figure 2).

Examining all groups together, there was no correlation between QRS duration and RV mass (Figure 3a). When analyzing the groups separately, the tetralogy of Fallot group showed a significant correlation between QRS duration and RV mass ($r=0.67$; $p=0.01$), (Figure 3b). In patients with tetralogy of Fallot and ccTGA, we found a significant correlation between RVEDV and RV mass ($r=0.91$; $p=0.001$ and $r=0.82$; $p=0.007$, respectively).

**BRAIN NATRIURETIC PEPTIDE**

BNP levels were increased in all patient groups (table 2) compared to reference values$^{10}$. No significant correlation between BNP plasma levels and ECG parameters was found. In the line with our previous results$^{10}$, no correlation was found between BNP plasma levels and RV systolic pressure. A weak correlation was found between BNP and RVEDV; $r=0.59$; $p=0.004$.

**DISCUSSION**

**MAIN FINDINGS**

Our data show a prolongation in QRS duration and QRS dispersion over time in patients with chronic RV pressure overload, regardless of the nature of congenital heart disease. This is the first study exploring changes in ECG markers over time in patients with chronic RV pressure overload due to congenital heart disease. In the studied population, RVEDV, RV mass, and BNP were increased compared to the known reference values for healthy volunteers. A significant correlation was found between QRS duration and RVEDV, in patients with a
subpulmonary RV submitted to chronic pressure overload\textsuperscript{1,14}. With this study, we demonstrated a significant correlation between QRS duration and RV mass in tetralogy of Fallot patients.

**QRS DURATION**

Several studies described the importance of QRS duration and dispersion as a predictor of dangerous tachycardias and sudden death in patients with congenital heart disease\textsuperscript{3,5,6,14-17}. In tetralogy of Fallot patients, QRS>180 ms is a strong predictor for malignant VTs\textsuperscript{3,6}. The exact length of QRS prolongation that predicts VT may be variable\textsuperscript{5}. Only 6 patients from our study had QRS>180 ms. Four patients showed non-sustained VTs, (only one patient had QRS > 180 ms), all lasting less than 3 seconds. We observed an increase of QRS duration over a period of 5 years in all patient groups, however, significant in the ccTGA and in the subpulmonary RV patient group. Our findings emphasize the need of consequent follow-up of ECG parameters in these patients.

**QRS DISPERSION**

In the period of 5 years, QRS dispersion increased significantly in patients with surgically corrected TGA and tetralogy of Fallot. Gatzoulis et al.\textsuperscript{3} introduced QRS dispersion as a marker to study inhomogeneity of ventricular depolarization, and showed the presence of depolarization abnormalities in patients with tetralogy of Fallot. These are significantly greater in patients with sustained VT and a QRS>180 ms, than in patients without VT and with a QRS<180 ms\textsuperscript{3}. In our population with increased QRS dispersion (n=17), we found only 1 patient with non-sustained VT, and 2 with QRS>180 ms. Most of the examined patients had QRS<180ms. However, according to the findings of Gatzoulis et al\textsuperscript{3} the significant increase in QRS dispersion in our patient groups with surgically corrected TGA and tetralogy of Fallot, could have important clinical implications concerning the risk of development of malignant VTs.

![Figure 3](image.png)

*Figure 3.* Correlation between QRS duration and right ventricular (RV) mass in patients with chronic RV pressure overload. ccTGA, congenitally corrected transposition of the great arteries; TOF, tetralogy of Fallot; TGA, surgically corrected transposition of the great arteries; rest: 9 patients with residual pulmonary valve stenosis, 4 with peripheral pulmonary stenosis, 1 with primary pulmonary hypertension. Total, all patients groups together. A) correlation between QRS duration and RV mass in all patient groups, B) correlation between QRS duration and RV mass in patients with TOF.
ECG PARAMETERS AND RVEDV
We found a significant correlation between QRS duration and RVEDV in our patient population. The strongest correlation was found in the group of patients with subpulmonary RV, functioning under chronic pressure overload. An association has been reported between ventricular enlargement secondary to pulmonary regurgitation and a prolonged QRS duration on surface ECG, as a predictor of ventricular arrhythmias\(^1\). In that study, the authors used the plain chest X-ray for RV size determination. Similar findings have been reported by Rahman et al.\(^{14}\) using echocardiography for RVEDV determination in patients with tetralogy of Fallot. By applying newly available three-dimensional imaging technique like MRI and 3 dimensional echocardiography, determination of RV volume in patients with congenital heart disease has become more reliable. Daliento et al.\(^{1}\) using echocardiography in patients with tetralogy of Fallot observed that RVEDV and QRS duration are significantly associated with SVT or ventricular fibrillation. The authors concluded that RVEDV is the most significant marker of malignant ventricular arrhythmias.

Our results suggest that RVEDV and QRS duration are correlated, and may progressively increase over time. A close follow-up of both parameters is therefore of clinical importance in these patients.

A significant correlation was found between RVEDV and RV mass in patients with tetralogy of Fallot and ccTGA. A similar correlation has already been described by Grossman et al., for left ventricular eccentric hypertrophy\(^{18}\).

ECG PARAMETERS AND RV MASS
For the first time, we have demonstrated a significant correlation between RV mass and QRS duration in patients with tetralogy of Fallot; increased mass is most probably due to RV hypertrophy. No correlation was found between RV mass and QRS duration in patients with surgically corrected TGA or ccTGA. In these patients, the RV supports the systemic circulation from the earliest stages of cardiac development, and the increase of RV mass is most probably the result of hyperplasia\(^{19,20}\).

ECG PARAMETERS AND BNP
The possible relation between plasma neurohormone BNP levels and ECG parameters was examined. Raised plasma levels of BNP have been reported previously in patients with LV systolic dysfunction\(^{12,21,22}\). Tsutamoto et al.\(^{23}\) stated that a high BNP level may predict mortality and morbidity in asymptomatic patients with LV dysfunction. The relation between neurohumoral factors and RV function so far has received little attention\(^{10,11}\).

The patients we studied were asymptomatic or slightly symptomatic. Although our patient population had higher mean BNP plasma levels compared to control healthy volunteers\(^\text{10}\) we found no significant correlation between plasma BNP and ECG parameters. In these asymptomatic patients, ECG changes are probably related to anatomic changes such as ventricular volume and postoperative scars, while BNP plasma levels most probably are related to RV function\(^\text{10}\). At this moment, the clinical consequences of these results remain speculative, as follow-up data of the variation in plasma neurohormone levels over time needs yet to be studied.

STUDY LIMITATIONS
Examination of small groups entails loss of statistical power and therefore, the present report requires confirmation in larger groups of patients. Furthermore, all patients were asymptomatic.
or slightly symptomatic. Follow-up of these patients will be necessary to learn more about the prognostic significance of the quantitative determinants examined in this study.

CONCLUSIONS

Our study shows a gradual worsening of ECG parameters in asymptomatic or minimally symptomatic patients with chronic RV pressure overload, regardless of the nature of congenital heart disease. In all patients, a positive significant correlation was found between QRS duration and RVEDV. In patients with tetralogy of Fallot, a significant correlation was found between RV mass and QRS duration. No correlation was found between QRS duration and plasma BNP levels.
REFERENCES


