Prognostic significance of right ventricular extrasystoles

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Abstract
Extrasystoles (RVES) from the right ventricular outflow tract (RVOT) are a common arrhythmia in routine ECGs.

Methods
In this prospective study 56 consecutive patients with RVES (22 males, 34 females) were examined for morphological and/or functional right ventricular (RV) abnormalities by 12-lead, Holter, exercise ECGs, transthoracic echocardiography and signal averaging. The follow-up time was 3.1–15.8 years (arithmetic mean ± SD = 7.2 ± 1.6 years; median, 6.9 years). Patients with hyperthyroidism, structural cardiovascular and/or lung diseases were excluded.

Results
A total of 57.1% of the patients with RVES presented with echomorphologic abnormalities of the right ventricle (RV). In 26.8% the echomorphologic right ventricular abnormalities progressed in 33.3% of patients with normal RVs at baseline (group I) and in 21.9% of those with abnormal RVs at baseline (group II). No significant differences were found between the 2 patient groups in terms of age at onset, family history, ECG changes, late potentials and malignant right ventricular outflow tract arrhythmias on 24-h and exercise ECGs. While females predominated in group I, males were numerous in group II (p = 0.006). Sustained ventricular tachycardia, syncope or sudden death were absent throughout the follow-up.

Conclusion
Patients with RVES carry a good prognosis in terms of morbidity and mortality no matter whether echomorphologic abnormalities are present or not.

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KEYWORDS
extrasystoles from the right ventricular outflow tract; structural/functional abnormalities; prognosis

Introduction

Right ventricular extrasystoles (RVES) with a left bundle branch block pattern and a vertical electrical axis are often seen in routine 12-lead ECGs. Patients with RVES are either asymptomatic or are
referred for further evaluation to a specialized unit because of palpitations, vertigo, presyncope or syncope.

To the best of our knowledge the predictive potential of these arrhythmias for the development of malignant arrhythmogenic events has not been evaluated prospectively in the literature.

In this prospective long-term study patients with RVES were examined for echomorphologic changes in the right ventricle, their progression and the arrhythmia profile.

Method

Fifty-six consecutive patients with RVES (22 males and 34 females), who were referred to our outpatient department because of symptoms or RVES seen in the routine ECG, were recruited for a prospective study. Patients were eligible for enrolment if their 12-lead ECGs showed monomorphic RVES up to a maximum of 3 consecutive beats. Patients with hyperthyroidism, structural cardiovascular and/or pulmonary diseases were excluded.

At baseline and at the clinical follow-up visits the history of the patients’ symptoms was taken and a physical examination was performed. Instrumental studies consisted of 12-lead ECG, exercise ECG, 24-h ECG, signal-averaged ECG and transthoracic echocardiography. Clinical follow-up visits were scheduled at intervals of 2–3 G 0–6 years (median, 1.8 years). The mean follow-up time was 7.2 ± 1.6 years (median, 6.9 years; range, 3.1–15.8 years).

Echocardiography

Complete bidimensional M-mode and Doppler scans were obtained in real time and frame by frame using an ALOKA SSD system and a 2.5 or 3.5 MHz transducer. Three scans were recorded from the right ventricular outflow tract (RVOT) from 3 different transducer positions at the parasternal long axis view, the parasternal short axis view of the right ventricular anterior wall at aortic root and pulmonary valve level. Three measurements were taken from the right ventricular inflow tract (RVIT) in the 3rd or 4th intercostal space at the subtricuspid region in the parasternal 2- and 4-chamber view and at the parasternal tricuspid short axis view as published by Foale et al. [1]. Scans were analyzed for abnormalities of wall motion at sites of predeletion. Measurements were made in end-diastole at the onset of the R wave in simultaneously recorded ECGs leading edge to leading edge. For analysis 3 different measurements in each transducer position were averaged.

The right ventricle was considered to be abnormal, if at least 2 measurements were above normal and/or if local morphologic changes were present.

For evaluation of the reliability of echocardiographic measurements 18.2% of all echocardiograms were evaluated by 2 independent observers. Corresponding values of the interobserver validated measurements were detected in 100% of patients with normal right ventricles and in 88% of patients with right ventricular abnormalities.

Signal-averaged ECG (ART 1200 EPX)

For signal averaging of the bipolar orthogonal leads x, y, z a bidirectional 40 Hz filter was used. Two of the 3 criteria mentioned below suggestive of late potentials had to be present [2]:

1. QRS > 114 ms.
2. Mean amplitude in the last 40 ms (RMS 40) > 20 µV.
3. Mean terminal low-amplitude signals (LAS) > 38 ms.

Twenty-four-hour ECGs were evaluated with Pathfinder 700 (Reynolds).

Statistics

Data are expressed as medians or arithmetic means ± standard deviations. Multivariate analyses were run on the statistics software Statgraphics 3.0. Differences were considered to be statistically significant at \( p < 0.05 \).

Results

Patient data

The mean age at onset was 40.3 ± 13.9 years (median, 39 years; range, 13–66 years), that of the females was 41.1 ± 13.4 years and that of the males was 27.0 ± 9.9 years (Table 1). The male:female ratio of the total population was 39.3% males versus 60.7% females. Forty-four patients (78.6%) had a non-contributory family history of malignant ventricular arrhythmias. Six patients (10.7%) reported sudden deaths and another 2 (3.6%) palpitations in the family. Two patients (3.6%) had family members undergoing treatment for malignant ventricular arrhythmias. Twenty-nine patients (51.8%) had palpitations, 10 patients (17.9%) had palpitations and atypical chest pain, 6 patients (10.7%)
experienced presyncope and 2 (3.6%) syncope. Nine patients (16.1%) had no symptoms.

The 12-lead ECG (Table 2)

The 12-lead ECG showed delayed right ventricular conduction in 9 patients (16.1%), abnormal repolarisation (negative T in V1–V3) in the right ventricular leads in 4 patients (7.1%) and left bundle branch block in 1 patient (1.8%).

The 24-hour ECG (Table 2)

The number of single RVES per 24 h in group I was arithmetic mean ± SD = 3330 ± 14, median, 80 beats; in group II arithmetic mean ± SD = 5472 ± 2485, median, 1847 beats, with no diurnal prevalence of RVES.

In 20 patients (35.7%) the Holter ECG showed couplets and in 6 (10.7%) triplets were present. Two patients (3.6%) presented with asymptomatic non-sustained ventricular tachycardia.

Ergometry (Table 2)

Nine patients (16.1% of the study population) developed couplets and 3 (5.4%) showed triplets during exercise.

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**Table 1** Demographics and history

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 24)</th>
<th>Group II (n = 32)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td><strong>Age at onset</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>40.3 ± 13.9</td>
<td>39.2 ± 13.6</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>39.0 years</td>
<td>38.0 years</td>
<td></td>
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<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (12.5%)</td>
<td>19 (59.4%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Female</td>
<td>21 (87.5%)</td>
<td>13 (40.6%)</td>
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<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>2 (8.3%)</td>
<td>7 (21.9%)</td>
<td>ns</td>
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<tr>
<td>Palpitations</td>
<td>17 (70.8%)</td>
<td>12 (37.5%)</td>
<td></td>
</tr>
<tr>
<td>Palp + presyncope</td>
<td>1 (4.2%)</td>
<td>5 (15.6%)</td>
<td></td>
</tr>
<tr>
<td>Palp + syncope</td>
<td>0</td>
<td>2 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>Palp + atyp chest pain</td>
<td>5 (20.8%)</td>
<td>5 (15.6%)</td>
<td></td>
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<tr>
<td><strong>Positive family history</strong></td>
<td></td>
<td></td>
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<tr>
<td>Palpitations</td>
<td>0</td>
<td>2 (6.3%)</td>
<td>ns</td>
</tr>
<tr>
<td>Documented VT</td>
<td>1 (4.2%)</td>
<td>1 (3.1%)</td>
<td></td>
</tr>
<tr>
<td>Sudden death</td>
<td>1 (4.2%)</td>
<td>5 (15.6%)</td>
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</tbody>
</table>

**Table 2** Investigations

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 24)</th>
<th>Group II (n = 32)</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>ECG</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Normal</td>
<td>20 (83.3%)</td>
<td>22 (68.8%)</td>
<td>ns</td>
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<tr>
<td>IRBBB</td>
<td>3 (12.5%)</td>
<td>6 (18.8%)</td>
<td></td>
</tr>
<tr>
<td>LBBB</td>
<td>0</td>
<td>1 (3.1%)</td>
<td></td>
</tr>
<tr>
<td>Neg T V1–V3</td>
<td>1 (4.2%)</td>
<td>3 (9.4%)</td>
<td></td>
</tr>
<tr>
<td>Positive late potentials</td>
<td>9 (37.5)</td>
<td>6 (18.9)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Holter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lown 0–3</td>
<td>14 (58.3%)</td>
<td>14 (45.2%)</td>
<td>ns</td>
</tr>
<tr>
<td>Couplets</td>
<td>8 (33.3%)</td>
<td>2 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>Triplets</td>
<td>3 (12.5%)</td>
<td>3 (9.7%)</td>
<td></td>
</tr>
<tr>
<td>Ns VT</td>
<td>0</td>
<td>2 (6.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Ergometry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lown 0–3</td>
<td>18 (75%)</td>
<td>26 (81.3%)</td>
<td>ns</td>
</tr>
<tr>
<td>Couplets</td>
<td>6 (25%)</td>
<td>3 (9.4%)</td>
<td></td>
</tr>
<tr>
<td>Triplets</td>
<td>0</td>
<td>3 (9.4%)</td>
<td></td>
</tr>
<tr>
<td>Ns VT</td>
<td>0</td>
<td>0</td>
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</table>

**Echocardiography**

At baseline (Fig. 1) the right ventricular structure was entirely normal in 24 patients (42.8%) (= group I). Right ventricular abnormalities were present at baseline in 32 patients (57.1%) (= group II). Of these, 9 (16.1%) showed global dilatation (right ventricular outflow and inflow tracts), another 10 (17.8%) showed regional dilatation (right ventricular outflow tract in 6 pts, right ventricular inflow tract in 4 pts). Abnormal wall motion (bulges) was seen in 13 patients (23.2%). At the final visit (Fig. 2) the right ventricle was abnormal in 8 patients (33.3%) of group I. Of these, 2 (8.3%) presented with regional right ventricular dilatation. Five patients (20.8%) had developed abnormal wall motion (bulges). In 1 patient regional dilatation was combined with abnormal wall motion. Of the patients in group II, another 7 (21.9%) had developed further right ventricular abnormalities during the follow-up (Fig. 2). These included abnormal wall motion in 2 patients (6.3%), regional right ventricular dilatation in 1 patient (3.1%), global right ventricular dilatation in 2 patients (6.3%) and global dilatation with bulging in 3 patients (9.4%). Obvious progression of right ventricular inflow tract dilatation, which had already been present at baseline, was noted in 1 patient (3.1%). Right ventricular outflow tract dilatation was most severe in transverse parasternal scans (median, 4 mm) at the level of the aortic root. In longitudinal parasternal scans the median was 3 mm. RVOT dilatation was absent at the level of the pulmonary
valve. Right ventricular inflow tract (RVIT) dilatation was most severe on the apical 4-chamber view (median, 3 mm), on the apical 2-chamber view the median was no more than 1 mm. Transverse parasternal views at the level of the mitral valve failed to show RVIT dilatation. Left ventricular function was normal at baseline in all patients.

At the final visit left ventricular function was borderline (EF 50%) in 2 patients of group II (6.5%). In group I patients left ventricular function was normal throughout.

Late potentials (Table 3)

Signal-averaged ECGs of 51 patients (91.1%) were adequate for evaluation at a median noise level of 0.3 μV. Three patients (5.4%) were excluded because of incomplete right or left bundle branch block.

Late potentials were present in 15 patients (26.8%), i.e. 9 of group I (37.5%) and 6 of group II (18.8%). None of these patients was on antiarrhythmic medication.

Drug treatment (Table 4)

At baseline 12 patients (21.4%) were on drugs (group I, 20.8%; group II, 21.9%) versus 8 patients (14.3%) at the final follow-up visit (group I, 8.3%; group II, 18.8%). According to the published literature, drug therapy was only prescribed in patients with intolerable symptoms [7,53,54]. Medication was changed, if patients continued to suffer despite the first drug therapy. It was stopped, if patients had no or few symptoms. In no patient had we to change drug treatment because of malignant right ventricular outflow tract arrhythmias.

Mortality

During the follow-up time no sustained ventricular tachycardia, syncope or sudden death were recorded.

Discussion

Right ventricular outflow tract extrasystoles are often found to be present in 12-lead ECGs of oligo- or asymptomatic patients. To the best of our knowledge the prognostic significance of right ventricular extrasystoles and their relation to morphologic or functional abnormalities of the right ventricle has not been evaluated in a prospective study design.
This is the largest prospective study which related RVES to morphologic and/or functional right ventricular abnormalities and evaluated their predictive potential.

**Clinical manifestations in patients with RVES**

The age at onset of our patients was 13–66 years (median, 39 years). This agrees well with the age distribution reported in studies of patients who manifest malignant ventricular arrhythmias. The overrepresentation of women in the group with right ventricular abnormalities is of interest insomuch as the sex distribution of the consecutive patients enrolled in this study was similar to that reported for patients with arrhythmogenic right ventricular cardiomyopathy (ARVCM) [3–8].

As the family history was positive for arrhythmogenic events in 14.3% of cases, the patients in our study may well have had a benign variant of ARVCM. In fact, 83.9% of the symptoms elicited in our patients (palpitation, presyncope, syncope) may have been arrhythmogenic in origin.

The 2 patients with a history of syncope were subjected to electrophysiological studies: non-sustained ventricular tachycardia was shown in 1 case and normal ventricular vulnerability in the other. None of them experienced syncope during the follow-up of 103 and 41 months, respectively. Both long-term and exercise ECGs failed to show malignant ventricular arrhythmias. But both patients had right ventricular abnormalities, late potentials on signal-averaged ECGs and a positive family history. Whether or not these patients carried an increased risk can currently not be said. Also inducibility of ventricular arrhythmias does not allow any conclusion in regard to the prognostic value of RVES.

**Diagnostic criteria of patients with RVES**

Various invasive studies like myocardial biopsy, ventriculography, electrophysiology as well as such non-invasive studies as echocardiography, magnetic resonance imaging and SPECT are available for evaluating right ventricular pathophysiology [8–48]. But minimal right ventricular abnormalities continue to be a diagnostic challenge. To the best of our knowledge none of the studies available offers superior sensitivity and specificity for detecting minor global and/or regional dilatations or abnormal wall motion.

In the literature non-invasive studies have been favoured for the early detection of ARVCM [26–33]. Transthoracic echocardiography is a low-cost technique, which is in routine clinical use. But as the right ventricle lies behind the sternum, it is less accessible to ultrasound than the left ventricle so that the scanning time is prolonged. Precise measurements of the right ventricle critically depend on the conditions for ultrasound transmission. Adequate ultrasound windows enhance the sensitivity of the technique and make the results comparable with those of invasive studies [34]. Consequently, family members of patients with right ventricular cardiomyopathy have mainly been examined by echocardiography for right ventricular abnormalities [35–44]. Echocardiographic measurements of normal adult right ventricles published by Foale et al. [1] were used as reference values. Measurements at 3 different transducer positions were analyzed in RVOT and RVIT. This method was also used in several other reports [35–44]. Fatty degeneration of the myocardium associated with ARVC is best evaluated by MRI. But MRI fails to detect early ARVC without fatty degeneration. It has not been used in 2 recent studies [44,47], because there is no conclusive evidence of its usefulness in early ARVC and ARVC without fatty degeneration.

**Long-term follow-up of patients with RVES**

In this study patients with RVES were shown to carry a favourable prognosis irrespective of the echomorphologic abnormalities recorded from the right ventricle at baseline. This also applied to patients with progressive echomorphologic changes during the follow-up time. The echocardiographic data collected were similar to those reported by Nava et al., who found 64% of the family members of ARVC patients to present with segmental right ventricular abnormalities [44]. This cannot be confirmed by our study, simply because family members of our patients were not screened for right ventricular abnormalities. But the abnormalities found in resting, exercise, 24-h and signal-averaged ECGs were compatible with those reported in the literature. It is, however, of interest to note that epsilon waves were absent throughout in our entire patient population. This may perhaps have prognostic implications [45–47]. Like Metzger et al., we did not find any correlation between the severity of the echocardiographic and the electrocardiographic abnormalities [47]. The absence of sustained ventricular tachycardia all but rules out a comparison of the arrhythmia profiles with those reported by others because of the difference in the composition of the patient material. But,
significantly, Hermida et al. found late potentials to occur at a similar rate in the relatives of his ARVCM patients [48].

The basic problem addressed in this study was also different from that investigated by others. We compared patients with and without echocardiographic abnormalities at baseline for their arrhythmia profiles, morbidity and mortality during follow-up. The retrospective follow-up study of a non-consecutive patient material recently published by Gaita et al. is also not readily comparable with ours for several reasons [49]: 25.5% of his patients presented with structural cardiac pathology. Patients with extrasystoles other than those generated in the right ventricular outflow tract were also included, i.e. those with premature beats of septal origin. This is significant inasmuch as biopsy data showed the septum often to be spared by ARVCM [50–52]. In addition, all patients in this study had normal echocardiograms. This is probably due to the scanning technique used. In Gaita’s study the right ventricle was not scanned in 3 planes as usual [1,27,29] so that abnormalities, if any, may have been missed. Our study conclusively showed that there was no difference between the 2 patient groups in terms of the rate of arrhythmia and arrhythmogenic events during a mean follow-up time of 7.2 ± 1.6 years. Potential effects of drug treatment on the course our patients cannot altogether be disregarded. After all, 12 of our patients needed anti-arrhythmic medication mainly classes II, III and IV because of intolerable symptoms [53,54]. Lastly, an even longer follow-up may be necessary in order to know the true prognosis of these patients.

Summary

In long-term follow-up this prospective study shows a good prognosis for patients with RVES in terms of morbidity and mortality. The arrhythmia profile recorded by non-invasive studies was independent of the echocardiographic abnormalities present in our patients. Electrophysiological studies do not have a place in this patient population.

References


