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ORIGINAL RESEARCH ARTICLE

Appearance of QRS fragmentation late after Mustard/Senning repair is associated with adverse outcome

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ABSTRACT

Objective To evaluate if development of fragmented QRS (fQRS) complexes, a marker of inhomogeneous ventricular activation due to myocardial fibrosis, is associated with adverse outcome in adults after Mustard/Senning repair for d-transposition of the great arteries (d-TGA).

Methods Adults with atrial switch repair for d-TGA were selected from the database of a tertiary care hospital. Exclusion criteria were systemic right ventricular (RV) assist device or heart transplantation (HTx) before the age of 16, or fQRS already present at first visit to the Adult Congenital Heart Disease clinic. A blinded expert reader retrospectively analysed all available ECGs after the age of 16 for the presence of fQRS. The appearance of fQRS was modelled for each patient as a time-dependent variable. Cox regression was performed to assess the relationship between covariates and the composite endpoint of cardiovascular mortality, HTx or systemic RV assist device.

Results Records of 89 patients (34% female, 42% Mustard repair) were analysed. At latest follow-up, fQRS was noted in 26 patients (29%). Over a median follow-up time of 16.9 (IQR 12.6–22.9) years, the composite endpoint occurred in nine patients (10%). In multivariable Cox analysis, appearance of fQRS (HR 14.11; 95% CI 1.42 to 140.12) and development of severe RV dysfunction (HR 11.36; 95% CI 2.08 to 62.17) were significantly associated with the composite endpoint.

Conclusions Appearance of fQRS complexes on a 12-lead ECG is associated with adverse outcome in adults after atrial switch repair for d-TGA. In this population, fQRS detection might be a promising and easily implementable tool to identify patients at risk for adverse events.

INTRODUCTION

Many patients following Mustard or Senning repair for d-transposition of the great arteries (d-TGA) have survived into adulthood.[1–3] Progressive decline in systemic right ventricular (RV) systolic function and ventricular arrhythmias are major concerns in these patients.[4–6] Risk stratification remains complex.[7] Both a high RV afterload due to systemic pressures and a volume overload due to increasing regurgitation of the systemic atrioventricular valve (SAVV) can lead to worsening RV systolic function and development of heart failure.[8] An important contributor to the decline in clinical status is myocardial fibrosis.[9] The presence of focal myocardial fibrosis can be assessed with late gadolinium enhancement (LGE) cardiovascular MR (CMR).[10] The extent of LGE in the systemic RV of patients after atrial switch repair for d-TGA correlates with age, ventricular dysfunction, electrophysiological parameters and clinical events.[9 10] However, CMR imaging is costly and access is limited. Therefore, a further search for an easily implementable tool to identify patients at risk for adverse outcome is needed.

Fragmented QRS (fQRS) complexes on a 12-lead ECG reflect inhomogeneous activation of the ventricles by the presence of myocardial fibrosis or scarring, and have been linked to all-cause mortality and sudden cardiac death in patients with ischaemic cardiomyopathy.[11–13] fQRS is also closely associated with more extensive RV fibrosis and RV dysfunction in adults with repaired tetralogy of Fallot.[14 15] Recently, the extent of fQRS was shown to be superior to QRS duration in predicting all-cause mortality in adult patients with tetralogy of Fallot.[16] However, the predictive value of the appearance of fQRS, assessed by serial ECGs, in adults after atrial switch repair for d-TGA has never been investigated.

METHODS

Patient selection and data collection

The records of all patients with atrial switch repair for d-TGA were retrieved from the Paediatric and Adult Congenital Heart Disease (ACHD) database of the University Hospitals Leuven, a tertiary care centre in Belgium specialized in congenital heart disease. All files until March 2016 were retrospectively reviewed. Exclusion criteria were no follow-up in our centre after the age of 16, a patient file without retrievable ECGs, implantation of a systemic RV assist device or heart transplantation (HTx) before the age of 16, or fQRS already present at first visit to the ACHD clinic. Baseline variables were documented at the moment of the first visit to the ACHD clinic.

The study was conducted in compliance with the principles of the Declaration of Helsinki. The local institutional ethical review committee approved the study and waived informed consent. All authors had direct access to the raw and derived datasets.

ECG analysis

Resting 12-lead ECGs were analysed by an experienced investigator (BV) for the presence of fQRS complexes. The analysis was performed blinded for patient characteristics and endpoints. Standard resting 12-lead ECGs of good quality, at

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25 mm/s paper speed were used. Resting heart rate, QRS duration and QT interval were collected based on automated analysis by the GE Marquette 12SL ECG Analysis Program (GE Medical Systems, Menomonee Falls, Wisconsin, USA). The corrected QT (QTc) interval was calculated using the Fridericia formula.

Critical criteria for fQRS analysis are dependent on QRS duration; therefore, the ECG data were divided into three groups: QRS duration ≤100 ms, QRS duration >100 ms or active ventricular pacing. As the prevalence of incomplete right bundle branch block was high and to prevent overestimation of fQRS, the QRS duration cut-off was defined at 100 ms. In patients with QRS duration ≤100 ms, fQRS was defined as the presence of any RSR' pattern, ≥1 R prime or notching of R or S wave.[17 18] In the setting of a QRS duration >100 ms, fragmentation was defined as various RSR' patterns with or without a Q wave, with >2 R waves (R') or >2 notches in the R wave, or >2 notches in the downstroke or upstroke of the S wave.[19] A paced QRS complex was defined as a wide QRS complex (duration >120 ms and without any evidence of QRS fusion) initiated by a paced spike.[19] Fragmentation of a paced QRS complex was defined as the presence of >2 R' or >2 notches in the S wave.[19] Examples of fragmented and non-fragmented QRS complexes are given in figure 1. QRS fragmentation was considered present when recorded in ≥2 contiguous leads related to the perfusion territories of the major coronary arteries (anterior as V1 to V5; lateral as I, aVL and V6; and inferior as II, III and aVF).[17 18] Severe QRS fragmentation was defined as fragmentation criteria present in ≥5 leads.[16]

To evaluate the ease of implementing fQRS detection in daily practice, a novice in fQRS detection (FH) was trained in fQRS analysis with 20 example 12-lead ECGs and evaluated afterwards a randomly selected sample of 100 ECGs on his own.

Echocardiographic data

Protocols of comprehensive two-dimensional echocardiographic examinations, performed and analysed in our institution by senior cardiologists specialised in ACHD, were reviewed. Severity of SAVV regurgitation was semiquantitatively assessed by colour flow Doppler and was graded as none to mild, moderate or severe.[20] Systemic RV function and systemic RV dilatation were qualitatively assessed using an integrative multiview approach; impairment was graded as none to mild, moderate or severe.[21 22]

Outcome assessment

Outcome analysis focused on (1) the composite endpoint of cardiovascular mortality, HTx or systemic RV assist device implantation; (2) worsening systemic RV systolic function; and (3) symptomatic arrhythmias. Worsening RV function was defined as a one or two-step change in the echocardiographic assessment of systemic RV function. Arrhythmias were defined as symptomatic if antiarrhythmic medication was prescribed, cardioversion or ablation was performed or pacemaker/implantable cardioverter defibrillator (ICD) was implanted.[4]

Statistical analysis

Categorical variables are expressed as numbers and percentages. Continuous data are presented as mean±SD or as median (quartile 1–quartile 3 (IQR)). Data were tested for normal distribution with the Shapiro-Wilk test. Intraobserver and interobserver variabilities were assessed using Cohen's kappa coefficient. The intraobserver testing was performed 3 months after the initial evaluation.

The relationship between a covariate and the risk for each endpoint was assessed using univariable Cox proportional hazards models, with baseline and subsequent determinations of fQRS, the development of severe SAVV regurgitation, severe RV dysfunction and severe RV dilatation entered as time-varying covariates. Afterwards, a multivariable Cox regression (fitted by backward elimination using a threshold of $p<0.10$ for elimination) was performed. HRs are presented with 95% CIs. An extended Kaplan-Meier analysis was performed to assess the differences in event-free survival for the composite endpoint between the presence and absence of fQRS.[23] For this analysis, patients started in the fQRS absent group and were switched over to the fQRS present group after the appearance of fQRS; time 0 for both groups was defined as the first day of follow-up in each group. The time to the occurrence of the composite endpoint was documented in years, with censoring at the time of latest follow-up.

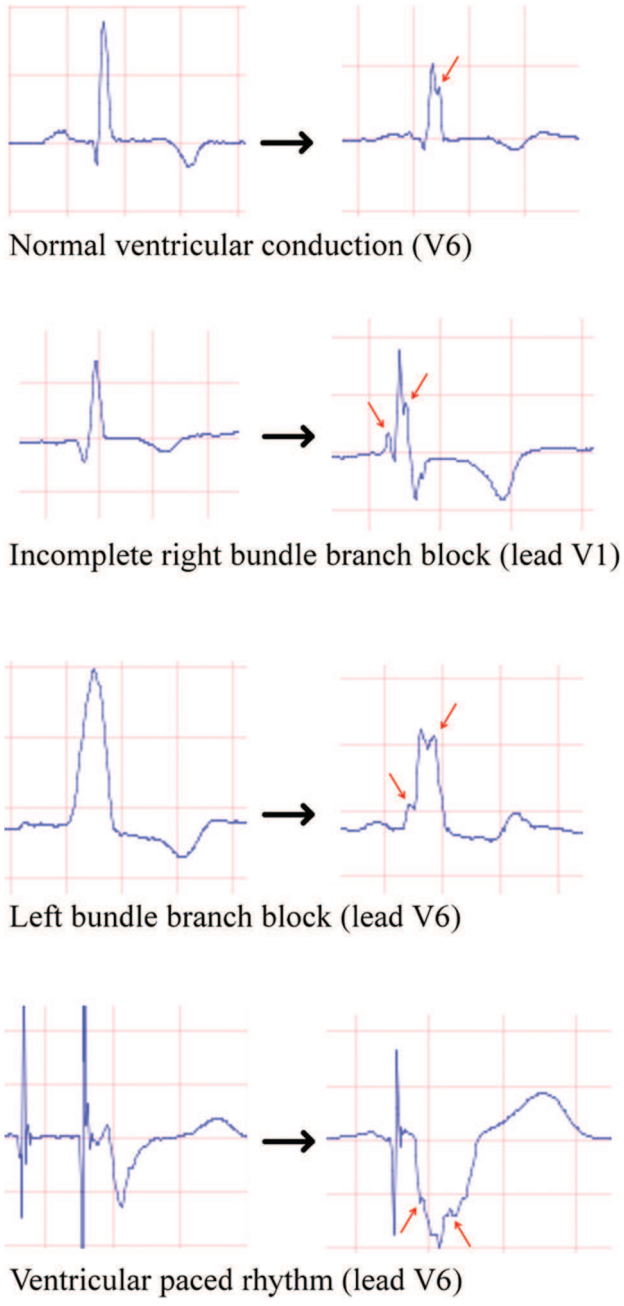

Figure 1 Evolution of a normal to a fragmented QRS complex (thin arrow = extra notch in QRS).

All statistical tests were two sided, and significance was defined as $p<0.05$. Analyses were performed using IBM SPSS Statistics, version 23.

RESULTS

Patient characteristics

The records of 133 patients were examined. After reviewing all records, 89 patients were found eligible and were included in the study (figure 2). Patients underwent atrial switch repair between October 1969 and November 1992; median age at repair was 0.5 (IQR 0.2–1.9) years. All patients operated before 1980 underwent Mustard repair. The demographics and baseline characteristics of the 89 patients are presented in table 1.

Appearance and severity of QRS fragmentation

During a median follow-up time in the ACHD clinic of 16.9 (IQR 12.6–22.9) years, fQRS was noted in 26 patients (29%). The mean age at which fQRS first appeared was 31.2±7.5 years. After the first appearance of fQRS, 10 patients (38%) developed severe fragmentation with a median interval between first appearance of fragmentation and development of severe fragmentation of 2.2 (IQR 0.6–4.8) years. Sixteen patients (62%) had no evolution in the extent of fragmentation; median follow-up after the detection of fQRS in this group was 4.5 (1.2–12) years. fQRS was most frequently found in the inferior lead (92%). The median of serial ECGs each study patient had available for analysis was 13 (IQR 8–23).

OUTCOME

Composite endpoint of cardiovascular mortality, HTx or systemic RV assist device implantation

The composite endpoint occurred in 10% of patients (table 2).

Table 1 Demographic and clinical variables at first visit to ACHD clinic

	Total population (n=89)
Age at first visit to ACHD clinic (years)	18.1 (16.7–22.2)
Age at atrial switch repair (years)	0.5 (0.2–1.9)
Mustard/Senning repair	37 (42)/52 (58)
Female gender	30 (34)
NYHA functional class (I/II/III/IV)	62 (70)/25 (28)/1 (1)/1 (1)
SAVV regurgitation (none to mild/moderate/severe)	57 (64)/26 (29)/6 (7)
Systemic RV dysfunction (none to mild/moderate/severe)	59 (66)/26 (29)/4 (5)
Systemic RV dilatation (none to mild/moderate/severe)	11 (12.5)/67 (75)/11 (12.5)
Heart rhythm (sinus/junctional/AF/PM)	85 (96)/1 (1)/1 (1)/2 (2)
Heart rate (bpm)	69±16
QRS duration (ms)	104 (94–115)
QTc (ms)	409 (393–433)

Units are listed as number (%), median (quartile 1–quartile 3) or mean ± standard deviation.

ACHD, adult congenital heart disease; AF, atrial fibrillation; QTc, corrected QT interval; n, number of patients; NHYA, New York Heart Association; PM, pacemaker; RV, right ventricular; SAVV, systemic atrioventricular valve.

Two patients were censored at the time of death because of a non-cardiovascular cause of death: one patient died during a car accident and the other due to sepsis. All other deaths were of cardiovascular origin (two died of advanced heart failure, one of a cardiac arrest during the induction of general anaesthesia and one out-of-hospital cardiac arrest). Two patients underwent HTx after initial systemic RV assist device implantation; in these patients only the implantation of a systemic RV assist device was included in the composite endpoint. On multivariable Cox

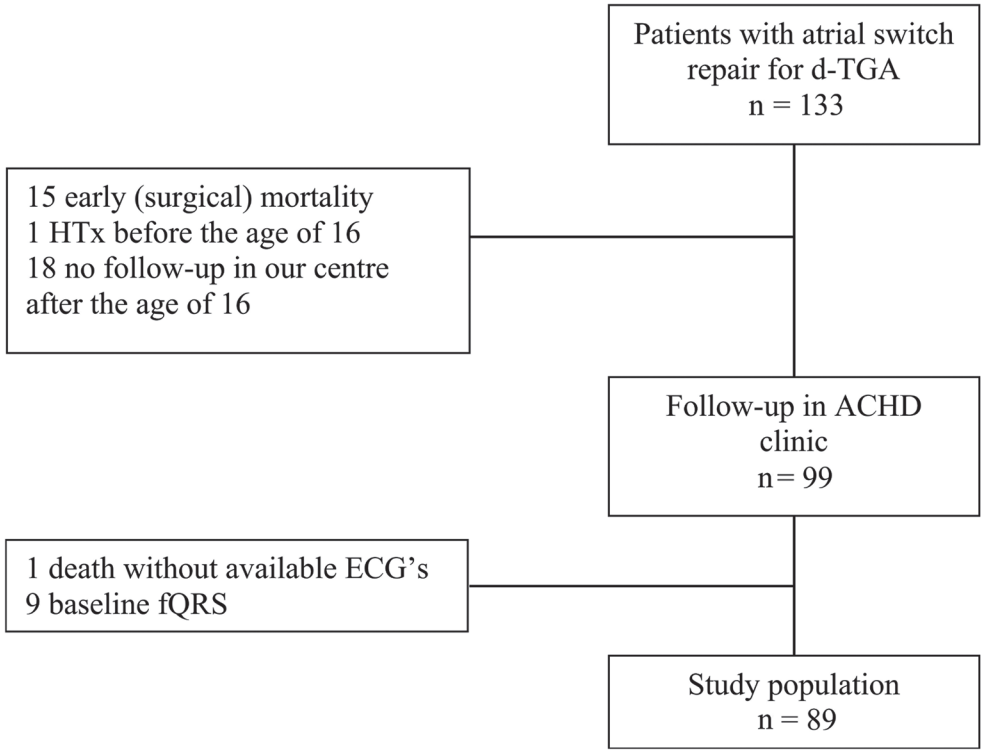

Figure 2 Flow chart to identify patients eligible for analysis. ACHD, adult congenital heart disease; d-TGA, d-transposition of the great arteries; fQRS, fragmented QRS; HTx, heart transplantation.

Table 2 Outcome and clinical variables at latest follow-up

	Events	Included in composite*
All-cause mortality	6 (7)	
Cardiovascular mortality, n/n (%)	4/6 (67)	4
HTx	4 (5)	2
Systemic RV assist device	3 (3)	3
Severe SAVV regurgitation or prosthetic valve	16 (18)	
Severe systemic RV dysfunction	16 (18)	
Severe systemic RV dilatation	26 (29)	
PM or ICD	13 (15)	
Symptomatic arrhythmia	30 (34)	

*In case of multiple events, the first event was included in the composite endpoint of cardiovascular mortality, HTx or systemic RV assist device.

Units are listed in number (%) unless otherwise indicated.

HTx, heart transplantation; ICD, implantable cardioverter defibrillator; PM, pacemaker; RV, right ventricular; SAVV, systemic atrioventricular valve.

regression analysis, appearance of fQRS in any major coronary artery territory and development of severe RV dysfunction were significantly associated with the composite endpoint (table 3).

The event-free survival was markedly worse when fQRS was present (figure 3). The median time from the detection of fQRS to a clinical event was 3.1 (IQR 0.6–6.8) years. In two patients, the ECG that demonstrated fQRS was taken 3 or 7 days before the implantation of a systemic RV assist device as a bridge to HTx. At the time of the composite endpoint, seven (78%) patients had severe fragmentation, one had moderate fragmentation and one had no fragmentation.

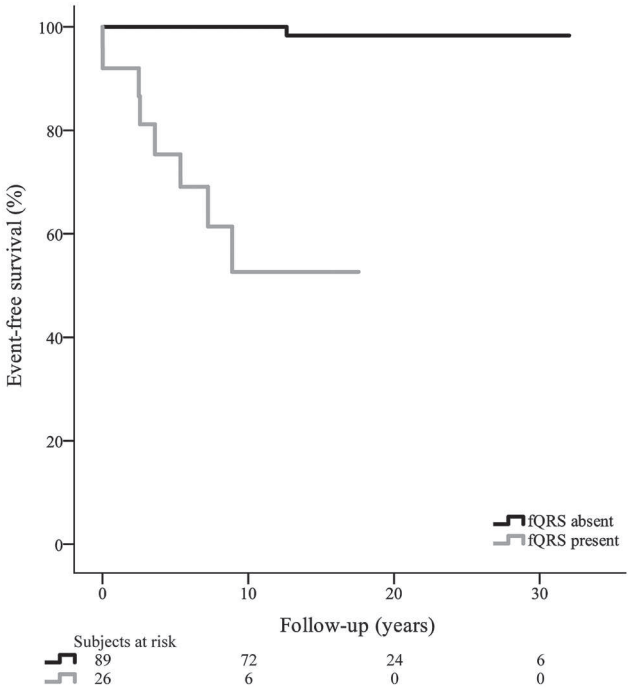

Figure 3 Event-free survival is worse when QRS fragmentation appears. Extended Kaplan-Meier analysis for the composite endpoint of cardiovascular mortality, heart transplantation or systemic RV assist device implantation. fQRS, fragmented QRS; RV; right ventricular.

Worsening systemic RV systolic function

During follow-up, worsening of systemic RV systolic function was noted in 42 patients (47%). Appearance of fQRS in any major coronary artery territory was, independently of development of severe SAVV regurgitation, significantly associated with worsening systemic RV systolic function. Patients who underwent Mustard repair were less likely to have worsening systemic RV systolic function during follow-up (table 4).

Symptomatic arrhythmias

Symptomatic arrhythmias occurred in 34% of patients. In 19 patients (63%), the first event was an atrial tachyarrhythmia. A pacemaker was implanted in 10 patients (4 with sick sinus syndrome, 4 with atrioventricular conduction problems and 2 with brady-tachy syndrome); ICD implantation was performed in three patients (one in secondary prevention after ventricular fibrillation and two with documented non-sustained ventricular tachycardia). Only Mustard repair was associated with the occurrence of first symptomatic arrhythmia (HR 3.62; 95% CI 1.51 to 867; p=0.004). The appearance of fQRS was not associated with the occurrence of symptomatic arrhythmias (HR 1.30; 95% CI 0.36 to 4.63; p=0.689).

Novice assessment of QRS fragmentation

There was a very good agreement between blinded novice and expert reading of fQRS. There was a 93.2% consensus in the 1100 analysed leads (κ=0.82, 95% CI 0.78 to 0.86, p<0.001). Three months after the initial assessment all leads were reassessed; intra-observer variability was excellent (κ=0.91, 95% CI 0.89 to 0.93, p<0.001).

DISCUSSION

The key findings of this study are that the appearance of fQRS in adults after atrial switch repair for d-TGA is (1) together with the development of severe RV dysfunction a strong independent predictor of adverse clinical outcome, (2) a predictor of

Table 3 Baseline and time-dependent variables related with the composite endpoint of cardiovascular mortality, heart transplantation or systemic RV assist device

	Univariable analysis			Multivariable analysis		
Variable	HR	95% CI	p Value	HR	95% CI	p Value
Appearance of fQRS	27.77	3.34 to 230.62	0.002	18.35	1.54 to 219.18	0.022
Development of severe RV dysfunction	28.88	6.18 to 135.01	<0.001	16.69	2.16 to 128.78	0.007
Development of severe RV dilatation	10.11	2.03 to 50.43	0.005			
Development of severe SAVV regurgitation	6.81	1.23 to 37.71	0.028			
Female	0.67	0.14 to 3.27	0.622			
Mustard repair	0.28	0.04 to 2.11	0.219			
Age at atrial switch repair	1.25	0.99 to 1.58	0.061	1.53	1.09 to 2.14	0.014

fQRS, fragmented QRS; RV, right ventricular; SAVV, systemic atrioventricular valve.

Table 4 Baseline and time-dependent variables related with worsening systemic RV systolic function

	Univariable analysis			Multivariable analysis		
Variable	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**
Appearance of fQRS	3.00	1.33 to 6.76	0.008	2.66	1.18 to 6.01	0.018
Development of severe RV dilatation	1.01	0.39 to 2.62	0.985			
Development of severe SAVV regurgitation	6.48	1.89 to 22.22	0.003	4.80	1.37 to 16.78	0.014
Female	1.16	0.61 to 2.18	0.655			
Mustard repair	0.25	0.12 to 0.52	<0.001	0.25	0.12 to 0.53	<0.001
Age at atrial switch repair	0.90	0.77 to 1.06	0.195			

fQRS, fragmented QRS; RV, right ventricular; SAVV, systemic atrioventricular valve.

worsening systemic RV systolic function and (3) not related with the occurrence of symptomatic arrhythmias.

Fibrosis and QRS fragmentation

Myocardial fibrosis, as detected by LGE, is seen in the systemic RV in about 50% of patients after atrial switch repair for d-TGA.[10 24] This may be due to preoperative cyanosis, surgical insult or long-standing pressure overload with subsequent excessive RV hypertrophy and demand-supply mismatch ischaemia.[10 24 25] fQRS is a well-established marker of myocardial scar, both in patients with coronary artery disease[18 19] and in patients with congenital heart defects.[14] Hypothesising that the appearance of fQRS could predict a patient's further clinical evolution, we modelled fQRS as a time-dependent variable. To the best of our knowledge, no previous study, neither in congenital nor in acquired heart disease, assessed fQRS in this longitudinal way. During a follow-up of 17 years, fQRS appeared in about one third of all patients. We hypothesise that fibrosis, as long as it is associated with fQRS, is not solely related to preoperative or perioperative damage in this population, but an ongoing process. fQRS appeared mostly in the inferior leads of the 12-lead ECG, corresponding to the perfusion territory of the right coronary artery. Although the origins and distribution of the coronary arteries are variable in d-TGA, the right coronary artery is the artery that perfuses the systemic RV.[26]

OUTCOME

Composite endpoint of cardiovascular mortality, HTx or systemic RV assist device implantation.

The appearance of fQRS was significantly associated with adverse clinical outcome. We choose strong clinical endpoints related to the performance of the systemic RV (ie, cardiovascular mortality and refractory heart failure leading to transplantation or implantation of a ventricular assist device). The hazard of experiencing such a clinical event was high when fQRS was present, even after adjusting for the development of severe RV dysfunction. The time from the detection of fQRS to a clinical event varied. In two patients, a systemic RV assist device was implanted (in retrospect) shortly after the detection of fQRS. This could question the clinical relevance of fQRS. However, in the other six patients the time from fQRS detection to a clinical event was more than 2 years.

Previous studies found, in patients with tetralogy of Fallot, an association between the extent of QRS fragmentation and the extent of LGE in the RV, RV systolic dysfunction or even all-cause mortality.[14–16] Our data are in line with these findings as most events were noted in patients with severe fragmentation. Moreover, some patients in our series had a progression of the extent of QRS fragmentation and some patients had stable fragmentation. It would be interesting for future studies to correlate the extent of fQRS with the degree of fibrosis on CMR and the systemic RV systolic function, and to evaluate this longitudinally.

Worsening systemic RV systolic function

When assessing worsening systemic RV systolic function, we found two relevant contributors. First, the development of severe SAVV regurgitation was associated with worsening systemic RV function. This supports the notion of the detrimental effect of an additional volume overload on the pressure-loaded systemic RV.[27] Second, the appearance of fQRS was also significantly and independently associated with worsening systemic RV systolic function. Surprisingly, patients who underwent Mustard repair had a lower likelihood for worsening systemic RV systolic function. We can only speculate about this finding. On the one hand, it could be a mere selection bias. All patients operated before 1980 underwent Mustard repair, later on almost all atrial switch procedures were Senning repairs. It is possible that in the early days of the atrial switch procedure only the best patients were operated, thereby making it a lower risk group for adverse events compared with patients who were operated when the experience of paediatric cardiologist, cardiac surgeons and anaesthesiologists allowed to operate patients with a worse clinical status. On the other hand, it could be that the systemic RV of patients after Mustard repair deteriorates more slowly because of less volume load due a restrictive filling pattern. Derrick *et al* effectively found in this population a failure to augment RV filling rates during exercise in the absence of other abnormalities of diastolic function.[28] This could lead to censoring of the patients, due to HTx or death, before the RV would deteriorate.

Symptomatic arrhythmias

When assessing the occurrence of a first symptomatic arrhythmia in our series, this endpoint was significantly associated with Mustard repair, as compared with Senning repair. Mustard repair can be considered an anatomical more aggressive repair. Some studies found a higher frequency of occurrence of sinus node dysfunction and sudden cardiac death after Mustard repair, whereas others did not observe a significant difference in arrhythmia-free survival.[3 6 29 30] Appearance of fQRS was not associated with the occurrence of symptomatic arrhythmias. This could be because this endpoint was mainly driven by atrial events. However, it is in contrast with a recent study by Rydman *et al*,[10] where ventricular fibrosis assessed by LGE CMR predicted atrial tachyarrhythmias. They observed atrial tachyarrhythmias in 19 (35%) of in total 55 patients with a mean age of 27±7 years and median follow-up 7.8 years (IQR 3.8–9.6 years). Although they reported on a shorter median follow-up, their findings will be largely influenced by the high prevalence of patients after Mustard repair (91%).

Clinical implementation

The detection of fQRS requires only a standard 12-lead ECG and some training on the correct assessment of the QRS. Effectively, after training on 20 ECGs, a novice reader could identify the presence of fQRS with a very high accuracy. We therefore consider this a relevant and easily implementable tool in daily practice.

STUDY LIMITATIONS

This study has some limitations. First, this was a retrospective, single-institution cohort study with a limited number of patients and events. The sample size and event rate were too small to assess the relationship between fQRS and ventricular arrhythmias. Second, routine clinical ECGs were visually interpreted for the presence of fQRS. Although interobserver variability between experienced readers has shown to be very low,[14 16] an automated analysis of the QRS could be of interest. Third, if no fQRS was present on the first ECG, regardless of the age of the patient, we assumed that at the age of 16 no fQRS would have been present. For statistical reasons, patients with fQRS at baseline ECG were excluded for further analysis. However, when including these patients in the Kaplan-Meier analysis, results remained unchanged. Fourth, we have no data on CMR markers of fibrosis in this cohort. Future research should be aiming at determining the critical amount of myocardial fibrosis necessary for observing fQRS.

CONCLUSIONS

The appearance of fQRS complexes on a routine 12-lead ECG in adults after atrial switch repair for d-TGA, as non-invasive marker of myocardial fibrosis, is associated with (1) cardiovascular mortality, HTx or systemic RV assist device implantation, and (2) worsening systemic RV function.

Key messages

What is already known on this subject?

Focal myocardial fibrosis is associated with adverse outcome in patients after atrial switch repair for d-transposition of the great arteries (d-TGA). Fragmented QRS (fQRS) complexes on a 12-lead ECG reflect inhomogeneous activation of the ventricles by the presence of myocardial fibrosis or scarring.

What might this study add?

De novo appearance of fQRS is associated with strong clinical endpoints related to the performance of the systemic right ventricle (ie, cardiovascular mortality and refractory heart failure leading to transplantation or implantation of a ventricular assist device).

How might this impact on clinical practice?

fQRS assessment on routine follow-up ECGs is an easily implementable tool in daily practice. Hence, diagnostic and treatment strategies can be adapted if fQRS is detected to anticipate potential adverse events. Moreover, linking the appearance of fQRS with clinical outcome can facilitate future research on fibrosis from both a basic science and myocardial imaging point of view.

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