Europace (2017) **0**, 1–7
doi:10.1093/europace/eux044

CLINICAL RESEARCH

Sudden cardiac death in adults with congenital heart disease: does QRS-complex fragmentation discriminate in structurally abnormal hearts?

Jim T. Vehmeijer[1], Zeliha Koyak[1], Jouke P. Bokma[1], Werner Budts[2], Louise Harris[3], Barbara J.M. Mulder[1,4], and Joris R. de Groot[1]*

[1]Department of Cardiology, Heart Center, Academic Medical Center—University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands; [2]Department of Cardiology, UZ Leuven, and Department of Cardiovascular Sciences, KU Leuven, Herestraat 49, B-3000 Leuven, Belgium; [3]Department of Cardiology, Toronto General Hospital, Toronto Congenital Cardiac Centre for Adults, 200 Elizabeth Street, M5G 2C4, Toronto, Ontario, Canada; and [4]Netherlands Heart Institute, Moreelsepark 1, 3511 EP Utrecht, The Netherlands

Received 9 December 2016; editorial decision 6 February 2017; accepted 6 February 2017

Aims Sudden cardiac death (SCD) causes a large portion of all mortality in adult congenital heart disease (ACHD) patients. However, identification of high-risk patients remains challenging. Fragmented QRS-complexes (fQRS) are a marker for SCD in patients with acquired heart disease but data in ACHD patients are lacking. We therefore aim to evaluate the prognostic value of fQRS for SCD in ACHD patients.

Methods and results From a multicentre cohort of 25 790 ACHD patients, we included tachyarrhythmic SCD cases ($n = 147$), and controls ($n = 266$) matched by age, gender, congenital defect and (surgical) intervention. fQRS was defined as ≥1 discontinuous deflection in narrow QRS-complexes, and ≥2 in wide QRS-complexes (>120 ms), in two contiguous ECG leads. We calculated odds ratios (OR) using univariable and multivariable conditional logistic regression models correcting for impaired systemic ventricular function, heart failure and QRS duration >120 ms. ECGs of 147 SCD cases (65% male, median age of death 34 years) and of 266 controls were assessed. fQRS was present in 51% of cases and 34% of controls (OR 2.0, $P = 0.003$). In multivariable analysis, fQRS was independently associated with SCD (OR 1.9, $P = 0.01$). The most common diagnose of SCD cases was tetralogy of Fallot (ToF, 34 cases). In ToF, fQRS was present in 71% of cases vs. 43% of controls (OR for SCD 2.8, $P = 0.03$).

Conclusions fQRS was independently associated with SCD in ACHD patients in a cohort of SCD patients and matched controls. fQRS may therefore contribute to the decision when evaluating ACHD patients for primary prevention of SCD.

Keywords Congenital heart disease • Sudden cardiac death • Fragmented QRS-complexes • Electrocardiogram • Risk stratification

Introduction

Adult congenital heart disease (ACHD) patients are at increased risk of sudden cardiac death (SCD).[1,2] SCD is difficult to predict, partly due to its relatively low overall incidence in ACHD patients, albeit manifold higher than in non-ACHD individuals of the same age. Even though many patients only have a mild defect, resulting in only a slightly increased risk of mortality and SCD, there is also a smaller number of high-SCD-risk patients with moderate to severe defects accompanied by ventricular scarring and ventricular dysfunction.[3]

* Corresponding author. Tel: +31 20 5669111; fax: +31 20 5669618. *E-mail address*: j.r.degroot@amc.uva.nl

Performed at the Department of Cardiology, Heart Center, Academic Medical Center—University of Amsterdam, Amsterdam, The Netherlands

What's new?

- fQRS has not previously been studied as a marker for sudden cardiac death in adults with congenital heart defects
- fQRS assessment in ECGs of adults with congenital heart disease is feasible and has a good intra-observer correlation
- fQRS was independently associated with sudden cardiac death, correcting for wide QRS complexes, impaired ventricular function and heart failure symptoms
- A risk model including fQRS may provide an improvement over one including only the traditional risk factors for sudden cardiac death

Nonetheless, considering all ACHD patients, up to one in every four of all deaths is due to SCD; a rate that closely follows heart failure: the number one cause of death in ACHD patients.[4–7] Although the evidence is limited, the risk factors for SCD in patients with acquired heart disease, such as impaired systemic ventricular function, QRS duration > 120 ms on the electrocardiogram (ECG) and heart failure symptoms, are also of prognostic value for SCD in ACHD patients.[4] Therefore, the indication for primary prevention of SCD in ACHD patients is often extrapolated from guidelines for patients with acquired heart disease.[7–9] In addition to aiding risk stratification for SCD, these parameters have also been shown to be associated with appropriate implantable cardioverter-defibrillator (ICD) interventions in ACHD patients.[10] However, independently, these clinical parameters are marginally prognostic.[4] Combining and increasing the number of risk factors is therefore likely to improve the accuracy of risk stratification tools. Therefore it is necessary to investigate additional markers for SCD in ACHD patients.

Fragmented QRS-complexes (fQRS) have been proposed as a prognostic sign of ventricular arrhythmia as well as SCD.[11] It is most likely caused by erratic activation paths inside ventricular scars, which may form a substrate for re-entry circuits.[12] Several studies report a clear association of fQRS with ventricular arrhythmia and SCD in patients with acquired heart disease.[11,13] However, the data on fQRS in ACHD patients are limited.[14,15] Moreover, scars in ACHD patients are more often caused by surgical cardiac ventriculotomy, rather than by infarction or other causes of fibrosis. In addition, patients with congenital heart disease often have wide and abnormal QRS-complexes. Therefore, the prognostic value of fQRS for SCD in patients with acquired heart disease cannot simply be extrapolated to ACHD patients. In this study, we assess the prognostic value of fQRS for SCD in a large cohort of ACHD patients who died of SCD, and their respective matched controls.

Methods

Study population

The study design and population of this study have been presented elsewhere in detail.[4] In short: this was an international, multicentre case control study of ACHD patients (≥18 years old). This study includes patients from three different cohorts of ACHD patients (total $n = 25\,790$): from the Netherlands CONCOR-registry, the Toronto Congenital Cardiac Centre for Adults and the University Hospital Leuven. All patients with proven or presumed (by exclusion of other causes) tachyarrhythmic SCD ($n = 171$) were included. SCD was defined as (i) proven or documented arrhythmic death, (ii) arrhythmic death by exclusion (instantaneous death or circumstances compatible with SCD, without disease that would lead to death in the near future, and the absence of a non-arrhythmic cause of death at autopsy) or (iii) arrhythmic death by default: abrupt loss of consciousness and absence of pulse, without further data.

Case control design

To improve statistical power with the available data, each SCD case was matched to a control in a 1:n ratio (up to three controls per case, depending on availability) by the following characteristics: (i) age (±5 years of corresponding SCD case), (ii) gender, (iii) congenital defect, (iv) type of surgical intervention (e.g. prior shunt, palliative or corrective surgery, valve replacements), (v) date of surgical repair (within 5 years of corresponding SCD case) and (vi) treating medical centre (when available).

Data collection

Medical records of included patients were reviewed, patient data were deidentified and entered into a database. One investigator (J.V.), blinded for clinical outcome of patients, assessed fQRS-complexes on the last standard 12-lead ECG before death in SCD cases, and in controls on the ECG recorded at the age closest to the age of death of their respective cases. We defined fQRS as ≥ 1 additional discontinuous deflection in the R- or S-wave in the QRS-complex or an additional R- or S-wave in narrow QRS-complexes, and ≥ 2 (i.e. one additional deflection, not part of the bundle branch block) in wide QRS-complexes (>120 ms), due to bundle branch block or ventricular pacing (*Figure 1*).[16,17] In ECG's with RSR' patterns in V1 and V2 and QRS-duration between 100 and 120 ms (incomplete right bundle branch block), we did not consider the additional R' to be fQRS. Finally, we only considered fQRS to be present when visible in ≥ 2 consecutive QRS-complexes in ≥ 2 contiguous ECG-leads. In addition to the binary variable of the presence of fQRS, we also

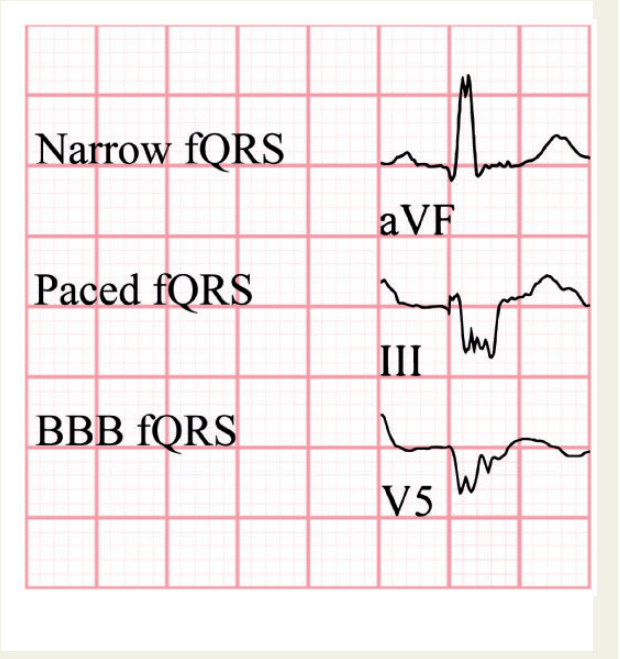

Figure 1 Examples of fQRS complexes. BBB, bundle branch block.

assessed the extent of fQRS by the number of ECG-leads in which fQRS was visible (none, moderate: in ≤ 4 ECG-leads, or extensive: in ≥ 5 ECG-leads). Furthermore, we analysed the prognostic value of the spatial position of fQRS: anterior (leads V2–V4), inferior (leads II, III and aVF), lateral (V5, V6, I and aVL) or other leads (V1 and aVR) and the temporal position of fQRS (onset, middle or end of the QRS-complex). To test interobserver variability, a second observer assessed fQRS on a random sample of 50 ECGs (J.B.)

Statistical analysis

We performed all data analyses with IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA) and R, version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria). We expressed descriptive statistics for nominal data in absolute numbers and percentages. For normally distributed continuous variables, we calculated mean values and standard deviations (SDs). We presented non-normally distributed data in medians and interquartile range (IQR). We used conditional logistic regression models for proportions, and for univariable and multivariable analysis of risk factors for SCD and displayed the results in odds ratios (OR) with 95% confidence intervals (CI). We generated receiver operating characteristic (ROC) curves with corresponding area under the curve (AUC) to display the discriminative power of risk stratification models. We used the intraclass correlation coefficient to determine interobserver variability in the observed number of ECG leads with fQRS. For all analyses, we considered two-tailed *P*-values < 0.05 to be statistically significant.

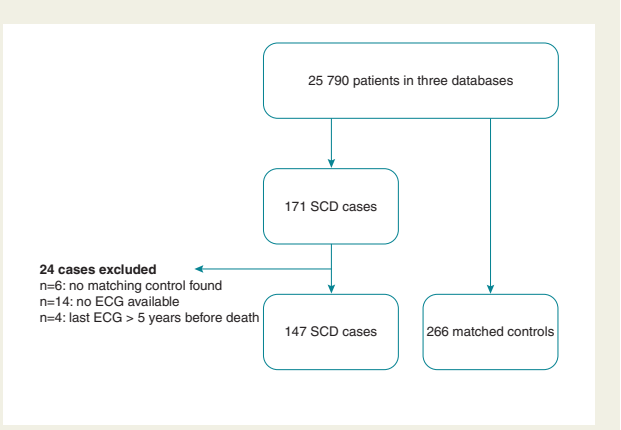

Figure 2 Flowchart of patient selection.

Results

We analysed a total of 147 SCD cases and their 266 respective controls. A flowchart of the patient selection is presented in *Figure 2*. The most common congenital defects among SCD cases were tetralogy of Fallot (ToF), univentricular heart (UVH) and transposition of the great arteries (TGA) (*Figure 3*). In SCD cases, the median time from the ECG to death was 128 days (IQR 52–437). Other characteristics of SCD cases and controls are displayed in *Table 1*.

Fragmented QRS

fQRS was present in the ECGs of 51% ($n = 75$) of SCD cases vs. 34% ($n = 91$) of controls. The OR for SCD in patients with vs. without fQRS was 2.0, 95% CI 1.3–3.1, $P = 0.003$. The interobserver correlation coefficient of fQRS was 0.85 [0.74–0.92].

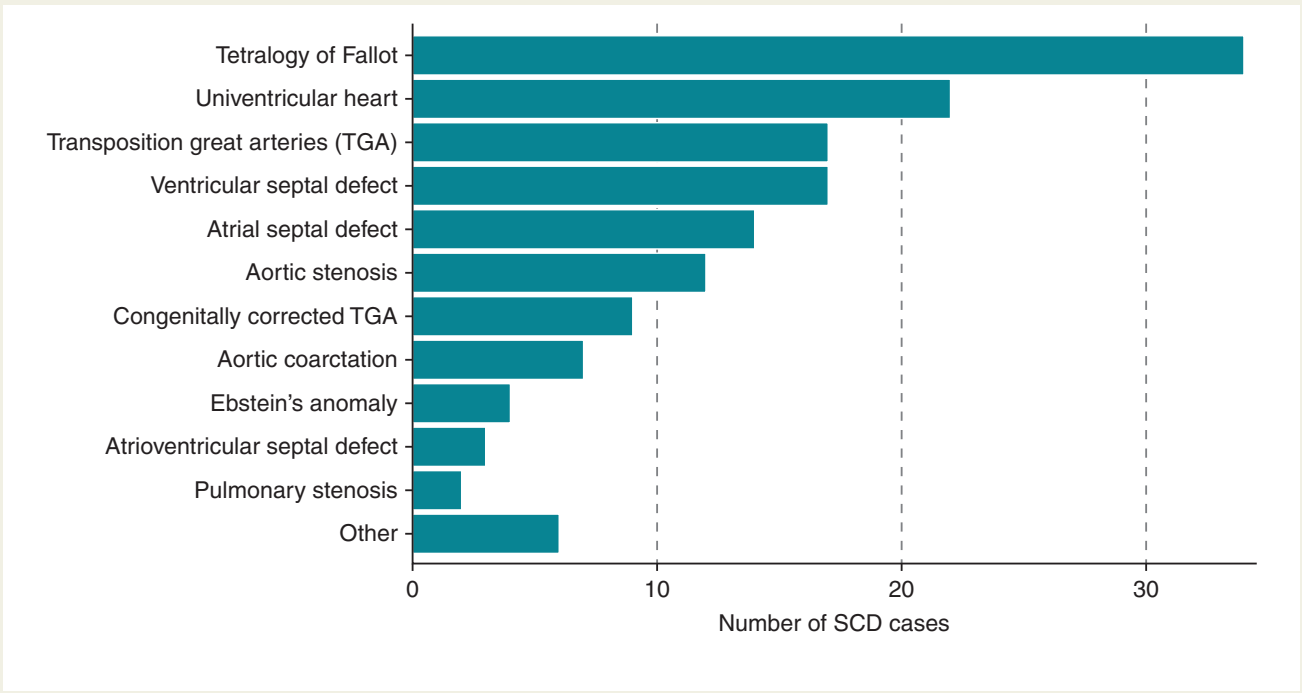

Figure 3 Congenital heart defects of sudden cardiac death cases ($n = 147$).

In patients with QRS complexes > 120 ms, 55% had fQRS, compared to 44% of patients with narrow QRS-complexes. In patients with a ventricular paced rhythm, 32% of patients had fQRS, compared to 42% without. When performing a subanalysis of 120 cases and 216 controls excluding cases (and their respective controls) with a ventricular paced rhythm, the odds ratio for SCD in patients with fQRS was 2.4 (95% CI 1.5–4.0, $P < 0.001$) compared to patients without fQRS.

In another subanalysis including only patients with an impaired systemic ventricular function, only 18 cases and their 24 controls remain, and the odds ratio for SCD in patients with fQRS is 9.9 (95% CI 1.3–78, $P = 0.03$). fQRS was not significantly associated with ventricular arrhythmias not directly causing SCD, i.e. non-sustained ventricular arrhythmia ($n = 47$) and sustained ventricular arrhythmia ($n = 5$): 47% of patients with ventricular arrhythmias had fQRS vs. 39% of those without (OR 1.38, 95% CI 0.76–2.5, $P = 0.29$).

In multivariable analysis of fQRS and SCD, adjusting for QRS width ≥ 120 ms, heart failure symptoms and impaired systemic ventricular function (ejection fraction ≤39%, or at least moderately impaired), fQRS remained independently associated with SCD (*Figure 4*).

Table 1 Characteristics of sudden cardiac death cases and matched controls

Characteristic	Case	Control	*P*-value
n	147	266	
Age, median [IQR]	34 [26, 49][a]	34 [27, 46][b]	
Female, *n* (%)	51 (35)	96 (36)	0.72
Impaired SVF, *n* (%)[c]	52 (36)	33 (13)	<0.001
Heart failure symptoms, *n* (%)	84 (57)	84 (32)	<0.001
QRS > 120 ms, *n* (%)	89 (61)	111 (42)	<0.001
Ventricular paced rhythm, *n* (%)	25 (17)	34 (13)	0.042

[a]Age at death.
[b]Age at ECG recorded at closest matching age to their respective case's age of death.
[c]SVF, Systemic ventricular function (ejection fraction ≤ 39% or at least moderately impaired).
IQR, interquartile range.

Assessing the extent of fQRS, 37% of SCD cases had moderate fQRS compared to 24% of controls, and 13% had extensive fQRS vs. 10% of controls. In multivariable analysis, there was no additional prognostic value of extensive fQRS for SCD compared to moderate fQRS: moderate fQRS vs. no fQRS, OR 1.9 (95% CI 1.2–3.1, $P = 0.008$), OR for extensive vs. no fQRS 2.1 (95% CI 1.1–4.4, $P = 0.04$).

Temporal and spatial organization of fQRS

Assessing the temporal position of fQRS in the QRS-complex, fQRS at the QRS-onset was significantly associated with SCD, as opposed to the middle or the end of the QRS-complex. fQRS in the anterior and lateral leads was significantly associated with SCD: anterior (21% in cases vs. 11% in controls, $P = 0.003$) and lateral leads (15% vs. 7%, $P = 0.02$), but not in inferior leads (29% vs. 23%, $P = 0.37$) or other leads (5% vs. 6%, $P = 0.71$). The results of the temporal and spatial position of fQRS are displayed in *Figure 5*.

Risk model including fQRS

When fQRS is added to a model including the conventional risk factors for SCD in acquired heart disease: impaired systemic ventricular function, heart failure symptoms and QRS > 120 ms, the AUC of the ROC curve increases from 0.78 to 0.80 (*Figure 6*).

fQRS in different congenital heart defects

We carried out subgroup analyses for the most prevalent diagnoses among SCD cases: 34 cases and 63 controls had ToF, and fQRS was present in 71% vs. 43%, respectively (OR 2.8, 95% CI 1.1–7.1, $P = 0.03$). Twenty-two cases and 37 controls had UVH and fQRS was present in 55% of cases vs. 30% of controls (OR 2.8, 95% CI 0.96–8.7 $P = 0.062$). Of all patients (22 cases and 42 controls) with a systemic right ventricle (SRV), i.e. TGA with Mustard or Senning repair and congenitally corrected TGA, 38% had fQRS, compared to 41% of those without SRV. fQRS was not significantly predictive of SCD in patients with SRV: fQRS was present in 50% of cases vs. 31% of controls, OR 2.3, 95% CI 0.77–7.1, $P = 0.134$).

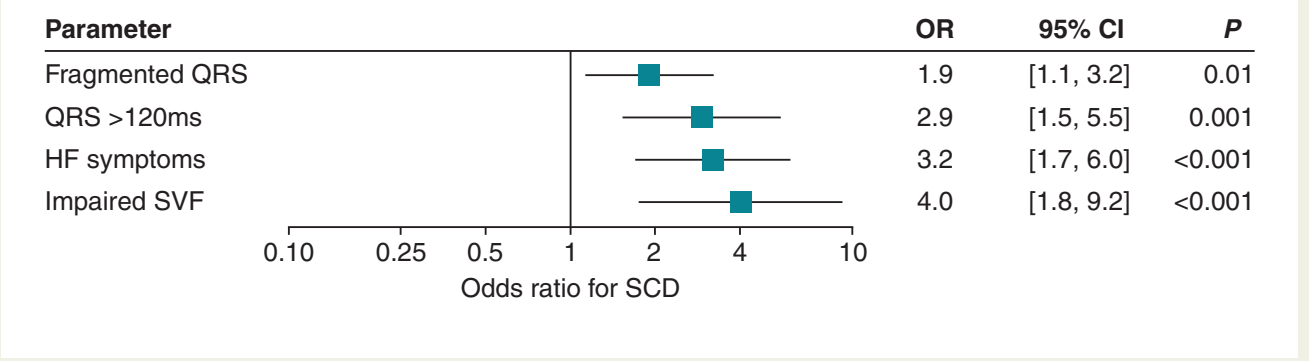

Figure 4 Multivariable logistic regression model of fQRS and SCD corrected for QRS width >120 ms, heart failure symptoms and impaired systemic ventricular function: ejection fraction ≤ 39% or at least moderately impaired.

Discussion

This case control study is the first study to show a clear association of fQRS with SCD in ACHD patients; fQRS was significantly more frequently found in patients who died of SCD than in matched living controls. Therefore, patients with fQRS may have a higher risk of SCD than those without, although addition of fQRS only provides a modest improvement over a model including only conventional risk factors for SCD. It may therefore serve as a parameter that reinforces a cardiologist's decision whether or not to implant an ICD. A

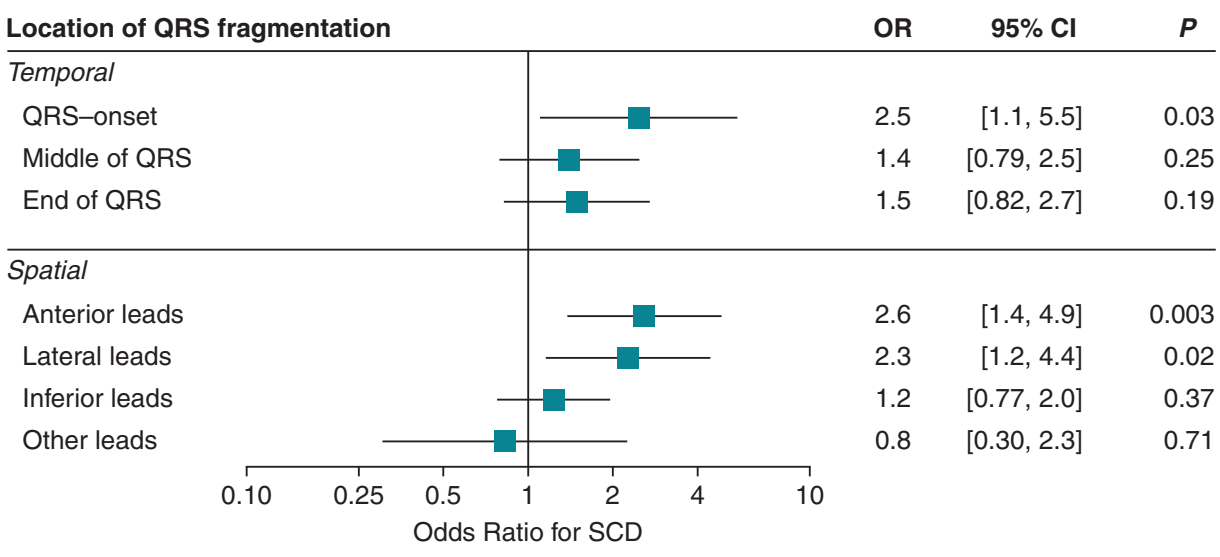

Figure 5 Temporal and spatial location of fQRS.

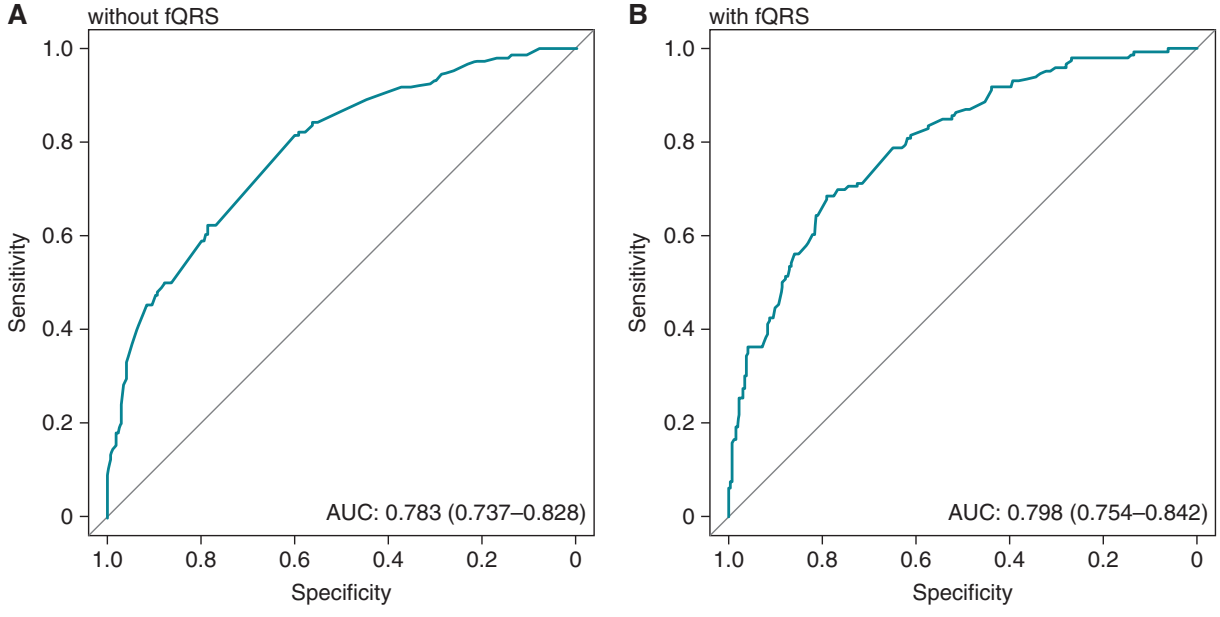

Figure 6 ROC curves of conditional logistic regression model including QRS > 120 ms, impaired systemic ventricular function (ejection fraction ≤39% or at least moderately impaired) and heart failure symptoms. (*A*) Without fQRS included in the model; (*B*) with fQRS included in the model.

benefit of fQRS is that it is easy to assess, and requires no added diagnostic testing, as ECGs are regularly recorded as part of usual outpatient care.

The prognostic value of fQRS appears to be mostly driven by its strong positive association with SCD in patients with ToF, which incidentally is the most prevalent diagnose among ACHD SCD cases. ToF patients are more likely to have larger and more ventricular scars, due to the extensive incision and patching that is needed for the surgical repair. Therefore, ToF patients may be more likely to have erratic activation paths through these surgical scars, causing fQRS and ventricular arrhythmia. fQRS is more strongly associated with SCD when present in the anterior leads (OR 2.1), compared to other regions of the heart. This may be explained by the often abnormal position and rotation of the heart inside the chest in ACHD patients, which may make it more difficult to accurately assess fQRS in the non-anterior regions of the heart. In this study, we found significant but likely not clinically meaningful differences when assessing the temporal position of fQRS. fQRS at the QRS-onset may be similar to pathological Q-waves. fQRS has a stronger association with SCD in patients without a ventricular paced rhythm (OR 2.4 vs. 2.0 in the overall analysis). Thus, fQRS may be more meaningful in patients without ventricular paced rhythm. In addition, fQRS was more strongly associated in patients with an impaired systemic ventricular function (OR 9.9), however, the numbers were likely too small to draw solid conclusions, so that this result may only be seen as hypothesis generating.

The patients in this cohort were matched, among other parameters, by surgical intervention. Therefore, the surgical ventricular scarring rate was likely to be similar in cases and controls. This indicates that fQRS is associated with SCD, irrespective of surgical intervention. However, since scarring is a probable substrate for SCD, the prognostic value of fQRS may increase when applied to unmatched patients, and requires further studying.

The association between fQRS and SCD appears to be similar in ACHD patients to that in acquired heart disease, i.e. ischemic and non-ischemic cardiomyopathy patients, in whom fQRS is also strongly associated with arrhythmic events and SCD. In a cohort of 361 patients, Das *et al.*[11] found an incidence of arrhythmic events of 55% in patients with fQRS vs. 10% in non-fQRS in two years. A recent meta-analysis found a risk ratio of 2.2 (CI 1.05–4.62) for SCD in acquired heart disease patients with fQRS, although a considerably more flexible definition of SCD was employed (SCD, resuscitated cardiac arrest, ventricular arrhythmia or appropriate ICD therapy) compared to the current study.[13] In congenital heart disease, the data are scarce. Although SCD has not previously been addressed, there are some data on ventricular arrhythmias in specific congenital defects: in a study of 51 Ebstein patients, 9/35 patients with fQRS had ventricular arrhythmias, compared to 0/16 patients without fQRS.[14] In a recent study on patients with ToF, Bokma *et al.*[15] found a hazard ratio for all-cause mortality of 3.11 for moderate vs. no fQRS and 5.84 for severe vs. no fQRS. In addition, fQRS was associated with ventricular arrhythmias with a hazard ratio of 2.0 per class. In our study, the extent of fQRS was not associated with SCD. Therefore, from a clinical perspective, it is reasonable to score fQRS as present (≥2 contiguous leads) or not present, when estimating the risk of SCD in ACHD patients, as proposed by Das *et al.*[16,17] for patients with acquired heart disease.

Limitations

Some limitations of our study warrant consideration. First, this was a retrospective analysis. Therefore, the inherent limitations to this study design apply. Second, documentation of heart rhythm at the time of death was not available for all cases; therefore it is not certain that all SCD cases were due to tachyarrhythmia. However, the definition for SCD used here conforms to the most frequently used clinical assessment. The databases from which the study population is derived had different inclusion periods, therefore the annual rate of SCD cannot be estimated accurately, and treatment strategies may have changed over time.

To our knowledge, the cohort reported on here is the largest cohort of SCD cases in ACHD patients to date. However, the number of SCD cases per congenital defect was small (*Figure 3*); therefore, this study is underpowered to draw conclusions on the prognostic value of fQRS for SCD in the rarer congenital defects. fQRS was not significantly associated with SCD in patients with TGA who had undergone Mustard or Senning surgery and congenitally corrected TGA patients (OR 2.3, $P = 0.134$). This is likely a cause of underpowering of the study with a limited number of patients with a SRV.

Lastly, the case-control design precluded us from providing positive and negative predictive values, as the prevalence of fQRS in the entire population of ACHD patients is unknown.

Conclusions

QRS-complex fragmentation is an independent marker for SCD in ACHD patients, although as a sole risk marker, its prognostic value is too limited to warrant ICD implantation. However, when combined with other clinical parameters, such as impaired systemic ventricular function, heart failure symptoms and wide QRS complexes, it may strengthen the indication for ICD implantation.

Acknowledgements

We thank the authors of the main study for their contribution to the database.[4] The work described in this study was carried out in the context of Parelsnoer Institute. Parelsnoer Institute is part of and funded by the Dutch Federation of University Medical Centers.

Conflict of interest: J.R.d.G. is supported by a VIDI grant from The Netherlands Organization for Health Research and Development (ZonMw/NWO, grant 016.146.310), and receives unrestricted research grants from St. Jude Medical and Atricure and is a consultant for Atricure and Daiichi Sankyo.

Funding

This was an investigator-initiated study. No specific funding was received for this study, other than from Academic Medical Center Medical Research BV.

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