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Baseline Fragmented QRS Increases the Risk of Major Arrhythmic Events in Hypertrophic Cardiomyopathy: Systematic Review and Meta-analysis

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Introduction: Fragmented QRS reflects disturbances in the myocardium predisposing the heart to ventricular tachyarrhythmias. Recent studies suggest that fragmented QRS (fQRS) is associated with worse major arrhythmic events in hypertrophic cardiomyopathy (HCM). However, a systematic review and meta-analysis of the

literature has not been done. We assessed the association between fQRS and major arrhythmic events in hypertrophic cardiomyopathy by a systematic review of the literature and a meta-analysis.

Methods: We comprehensively searched the databases of MEDLINE and EMBASE from inception to May 2017. Included studies were published prospective or retrospective cohort studies that compared major arrhythmic events (sustained ventricular tachycardia, sudden cardiac arrest, or sudden cardiac death) in HCM with fQRS versus non-fQRS. Data from each study were combined using the random-effects, generic inverse variance method of DerSimonian and Laird to calculate risk ratios and 95% confidence intervals.

Results: Five studies from January 2013 to May 2017 were included in this meta-analysis involving 673 subjects with HCM (205 fQRS and 468 non-fQRS). Fragmented QRS was associated with major arrhythmic events (pooled risk ratio =7.29, 95 % confidence interval: 4.00-13.29, $p < 0.01$, I^2=0%).

Conclusions: Baseline fQRS increased major arrhythmic events up to 7-fold. Our study suggests that fQRS could be an important tool for risk assessment in patients with HCM.

Abbreviations

fQRS	fragmented QRS
ICD	implantable cardioverter defibrillator
HCM	hypertrophic cardiomyopathy
MAE	major arrhythmic events

Introduction

Hypertrophic cardiomyopathy (HCM) is a common inherited disease of the heart muscle. The prevalence of the disease in the general population is approximately 1 in 500 (1). Some patients may remain asymptomatic throughout life but others may experience heart failure symptoms or sudden cardiac arrest. Symptomatic HCM is a now much more

manageable condition with improved options for SCA prevention (eg subcutaneous implantable defibrillator) and invasive treatments of outflow tract obstruction (1). Nonetheless, identification of patients at high risk of SCA or sudden cardiac death remains challenging.

The twelve-lead ECG is one of the most common, useful and cost-effective investigations performed in clinical settings. Fragmented QRS (fQRS) is a marker of myocardial scar and identifies high-risk patients in various cardiac conditions, including acute coronary syndrome, cardiac sarcoidosis, Brugada syndrome, acquired long QT syndrome, or idiopathic dilated cardiomyopathy (2-4). Recent studies suggest that fQRS is associated with increased major arrhythmic events in patients with HCM (5-9). However, no systematic review or meta-analysis of literature has been done to address the association in this group of patients. Therefore, we performed a systematicmeta-analysis to establish the association between fQRS and major arrhythmic events in HCM.

Method

Search strategy

Two investigators (CK and PC) independently searched for published studies indexed in MEDLINE and EMBASE databases from inception to January 2017 using a search strategy that included the terms “fragmented QRS”, “QRS fragmentation” and “hypertrophic cardiomyopathy” (described in online supplementary data). Only English language publications were included. A manual search for additional pertinent studies and review articles using references from retrieved articles was also completed.

Inclusion criteria

The eligibility criteria included the following:

(1) Cohort studies (prospective or retrospective) reporting incidence of major arrhythmic events (MAE) including sustained ventricular tachycardia, sudden cardiac arrest, or sudden cardiac death) in HCM patients with and without fQRS

(2) Relative risk, hazard ratio, odds ratio, incidence ratio, or standardized incidence

ratio with 95% confidence intervals or sufficient raw data for these calculations had to be provided.

(3) HCM participants without fQRS were used as controls.

Study eligibility was independently determined by two investigators (TR and NK) and differences were resolved by mutual consensus. Newcastle-Ottawa quality assessment scale was used to evaluate each study in three domains: recruitment and selection of the participants, similarity and comparability between the groups, and ascertainment of the outcome of interest among cohort studies (10).

Data extraction

A standardized data collection form was used to obtain the following information from each study: title of study, name of first author, year of study, year of publication, country of origin, number of participants, demographic data of participants, method used to identify cases and controls, method used to diagnose the outcomes of interest (fQRS and major arrhythmic events), and average duration of follow-up. Confounders were also assessed and adjusted effect estimates with 95% confidence interval 95% confidence intervals and covariates were included in the multivariable analysis.

To ensure accuracy, all investigators independently performed this data extraction process. Any data discrepancy was resolved by referring back to the original articles.

Statistical analysis

We performed a meta-analysis of the included cohort studies using a random-effects model. The extracted studies were excluded from the analysis if they did not present an outcome in each intervention group or did not have enough information required for continuous data comparison. We pooled the point estimates from each study using the generic inverse-variance method of Der Simonian and Laird (11). The heterogeneity of effect size estimates across these studies was quantified using the I^2 statistic and Q statistic. For the Q statistic, substantial heterogeneity was defined as $p<0.10$. The I^2 statistic ranges in value from 0 to 100% ($I^2<25\%$, low heterogeneity;

I^2=25%–50%, moderate heterogeneity; and I^2>50%, substantial heterogeneity) (12). A sensitivity analysis was performed to assess the influence of the individual studies on the overall results by omitting one study at a time. Publication bias was assessed using funnel plot and Egger's regression test (13) ($p<0.05$ was considered significant). All data analyses were performed using the Stata SE 14.1 software from StataCorp LP.

Result

Description of included studies

Our search strategy yielded 15 potentially relevant articles (8 articles from EMBASE and 7 articles from MEDLINE). After exclusion of three duplicate articles, 12 articles underwent title and abstract review. One article was excluded because it was an abstract presentation. Six articles were excluded at this stage since they were not cohort studies, did not report the outcome of interest (MAE) or were not conducted in patients with HCM, leaving five articles for full-length article review. Therefore, three retrospective and two prospective cohort studies of HCM patients (205 fQRS and 468 non-fQRS controls) were included in this meta-analysis. Figure 1 outlines the search and literature review process. The clinical characteristics and summary of included studies are described in Table 1.

Quality assessment of included studies

Newcastle–Ottawa scales of the included studies are described in the Supplement Table 1. The Newcastle-Ottawa scale uses a star system (0 to 9) to evaluate included studies on 3 domains: selection, comparability, and outcomes. Higher scores represent higher study quality. Intra-study risks of bias of included studies are also described in Supplement Table 2.

Meta-analysis results

Five studies from January 2013 to May 2017 were included in this meta-analysis. All of five studies did reveal an increased MAE among HCM patients with fQRS with four of the five studies achieving statistical significance. The pooled analysis demonstrated a statistically significant increased risk of MAE in HCM patients with

fQRS compared to non-fQRS HCM patients with the pooled risk ratio of 7.29 (95 % confidence interval: 4.00-13.29, $p < 0.001$, $I^2=0\%$). There was no statistical heterogeneity observed. Forest plot of our meta-analysis is shown in Figure 1.

Sensitivity analysis

To assess the stability of the results of the meta-analysis, we conducted a sensitivity analysis by excluding one study at a time. The results were not significantly altered indicating that our findings were robust.

Publication bias

To investigate potential publication bias, we examined the contour-enhanced funnel plot of the included studies in assessing change in log OR of death or composite outcome (Figure 2). The vertical axis represents study size (standard error) while the horizontal axis represents effect size (log odds ratio). From this plot, distribution of studies on both sides of the mean was symmetrical. The Egger's test was significant (p = 0.568) and confirmed no small study bias.

Discussion

Hypertrophic cardiomyopathy is a complex inherited heart disease and one of the most common causes of sudden cardiac death (SCD) in young adults. Multiple approaches to management of the patient should be taken into consideration. Prevention of SCD is a critical part of caring for the HCM patient. The overall risk of SCD in HCM patients is about 1% per year (14). Recommended prevention strategies include exercise restriction, anti-arrhythmic drugs, and ICD. Identifying those who would benefit from an ICD is challenging but an essential part of clinical decision-making. Recommendations are based on cohort studies that identify relationships between clinical characteristics and prognostic outcomes.

Our meta-analysis summarized all available evidence of MAE in HCM from five studies, a total of 779 patients. Fragmented QRS was present in 46% of the studied population. Our study revealed that HCM patients with fQRS have a statistically

significant increased risk of MAE compared to those without fQRS (pooled risk ratio of 7.29, 95% CI 4.00-13.29, p<0.001, I^2 = 0%). This result stresses the importance of integrating fQRS into risk stratification of HCM for SCD in clinical practice.

The importance of fQRS, which is suggestive of myocardial scarring and fibrosis, has been increasingly supported by recent studies of MAE in various cardiac diseases (2-4, 15, 16), including HCM (6, 15, 16). Fibrosis or tissue heterogeneity increases susceptibility to reentry and arrhythmias. The presence of fQRS is more common in patients with high-risk characteristics, such as family history of SCD, history of syncope, and HCM patients with a calculated HCM Risk-SCD score greater than 6%. (9) The strength of the association of fQRS with MAE may depend on observed territory of distribution(5, 7). A previous study of HCM patients found that the presence of fQRS in more than 2 territories has a positive predictive value of 33% and negative predictive value of 88% of MAE or sudden cardiac death (6).

Recently, HCM Risk-SCD, a tool developed to estimate the 5-year risk of SCD in HCM patients, was introduced to guide ICD placement for primary prevention of SCD (17). ICDs may be considered in patients with HCM Risk-SCD score of ≥4% to 6% 5-year risk and should be considered if 5-year risk ≥6%. Variables currently used in HCM Risk-SCD are age, family history of sudden cardiac death, unexplained syncope, left ventricular outflow gradient, maximum LV wall thickness, LA diameter, non-sustained ventricular tachycardia (17). fQRS could provide important additional risk assessment and in fact fQRS has been shown to increase the positive predictive value from 8% to 20% and specificity from 72% to 92% in patients with one risk factor (NEED REF). Specificity was increased from 88% to 94% in patients with at least two risk factors (7). Addition of fQRS to traditional markers significantly improved the specificity and positive predictive value of future MAEs in “low risk” patients as well (7).

Limitation

In our meta-analysis, there were some limitations that could limit its generalizability. First, all of the studies included were cohorts which are observational in

nature. Three out of five studies were retrospective. Secondly, our meta-analysis was only focused on MAE. Given the published outcomes available for study, we did not take overall mortality or total cardiovascular mortality into account. However, the recent study from Lu et. al. shows that fQRS is associated with increased all-cause mortality, cardiovascular disease mortality, and heart failure related death. (16) In addition, our data is not sufficient to determine the relationship between fQRS and other ECG parameters such as prolonged QTc or territory of fQRS to the outcome of interest. According to Debonnaire et. al., prolonged QTc is an independent predictor of ventricular arrhythmias and sudden cardiac death (6). Finally, there was some heterogeneity amongst the studies. However, we used sensitivity analysis methods in the random-effects model and found no difference betwern the imputed risk ratio and its 95% confidence interval.

Conclusion

In conclusion, we found that baseline fQRS significantly increased the risk of MAE in HCM patients. fQRS should be considered as an important factor when considering primary prevention ICD implantation in HCM patients. Further study is needed to establish the role of fQRS in risk stratification for SCD in patients with HCM.

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Figure legends

Figure 1 Search methodology and selection process

Figure 2 Forest plot of the included studies assessing the association between fragmented QRS and major arrhythmic events

Figure 3 Funnel plot of fragmented QRS and major arrhythmic events. Circles represent observed published studies

Supplementary material

Supplementary document 1 Search strategy and keywords

Supplementary table 1 Newcastle–Ottawa scales of the included studies

Supplementary table 2 Intra-study risks of bias of included studies

Table legends

Table 1 The clinical characteristics and summary of included studies

Table 1: Characteristics of included studies

Study	Debonnaire et al (6)	Femenia et al (5)	Kang et al (7)	Nomura et al (8)	Ozyilmaz et al (9)
Country	The Netherlands	Argentina, Spain, Belgium, Turkey, Venezuela, and Canada	South Korea	Japan	Turkey
Study design	Prospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Prospective cohort
Year of Publication	2015	2013	2014	2014	2017
Study subjects	HCM patient at Leiden University Medical Centre, The Netherlands	HCM patient with ICD implanted for primary or secondary prevention	HCM patient diagnosed from echocardiography between Feb 2001 and Apr 2007	HCM patient followed at the Kanazawa University Hospital and its affiliated hospitals from Sep 2008 to Mar 2010	HCM patients aged more than 17 who presented to the Mehmet Akif Ersoy Thoracic and Cardiovascular surgery Center, Training and Research Hospital and Bezmialem Vakif University School of Medicine between Dec 2012 and Mar 2016

Exclusion criteria	HCM patients with ventricular pacing or bundle branch block at baseline ECG	N/A	Reduced LV function (LVEF <50%), QRS <=120 ms, left or right bundle branch block, previous ICD placement (n and age <18 years	Unable to obtain appropriate ECG data at registration, clinical data missing, diagnosed with cardiac sarcoidosis after registration	Patients with previous history of aborted SCD or those who had previously undergone ICD implantation. Patients with history of septal ablation or myomectomy. Patients with hypertension, renal failure, history of MI or aoritic valve stenosis.
Number of subjects (% male, mean age)	195 patients (61% male, mean age 52 ± 13 years)	102 patients (52% male, mean age 41.16 ± 18.25 years)	273 patients (57% male, mean age 55 years)	94 patients (60% male, mean age 58 ± 17 years)	115 patients (58% male, mean age 46.5 ± 15.3 years)
Number of fQRS subjects	145	54	67	31	65
Number of non-fQRS subjects	50	48	100	63	50
Median LV wall thickness (mm)	21	24.79 ± 7.65	21 ± 4	17±5	N/A

Mean QTc duration (msec)	427 ± 28	430.38 ± 22.98	438 ± 29	436±36	N/A
LA size (mm)	N/A	42.72 ± 9.66	N/A	N/A	41.9±4.3
Hx of Non-sustained VT	52	39	N/A	N/A	N/A
Unexplained syncope	17	60	15	N/A	13
Family Hx SCD	91	33	33	**11**	48
Prior personal history of SVT/VF/ SCD	13	43	N/A	**7**	N/A
Abnormal BP during exercise	N/A	13	N/A	N/A	N/A
ICD implantation at baseline	58	102	N/A	7	11
fQRS definition criteria	Presence of various RSR' patterns, notching in the R or S wave or presence of >1 additional R in ≥2 beats of a	Presence of various RSR' patterns, which included an additional R' or notching of the R-wave, notching of the	Presence of an additional R', notching in the nadir of the R or S wave, or the presence of >1 R' in 2 contiguous leads that	**QRS duration <120 ms** R', notching in nadir of the S wave, notching of R wave, or >1 R' in 2 contiguous leads	Presence of R' with or without a Q wave on 12-lead ECG, the presence of notching on an R wave, the presence of

	non-aVR lead.	down- or upstroke of the S-wave, or the presence of >1R′ in two contiguous leads.	corresponded to a single myocardial territory.	**In patients with right or left bundle branch block (QRS duration ≥120ms)** RsR' pattern with or without a Q wave, >2 notches in the R wave, >2 notches in the downstroke or upstroke of the S wave, in 2 contiguous leads **Patients with mechanical pacing (QRS duration ≥120ms)** >2 R' or >2 notches in the S waves in 2 contiguous leads.	notching on an S wave, or the presence of more than one R' wave in two adjacent derivations corresponding to the feeding area of one of the major coronary arteries.
Endpoints	Occurrence of malignant sustained VT, VF, or SCD	Appropriate ICD therapies (sustained VT or VF)	Major arrhythmic events (sustained VT and SCD)	Major arrhythmic event (sudden cardiac death, sustained VT and VF)	Sudden cardiac death
Mean follow-up	Median 5.7 years (IQR 2.7-9.1)	47.9 ± 39.3 months	6.3 years	4 years	5 years

Conclusion	Extensive fQRS is associated with sustained VT/VF and or SCD in HCM patients.	fQRS is associated with a significant increase in arrhythmic events in HCM patients with ICD implant.	The presence of an fQRS, in particular in the inferior leads, was was significantly associated with a higher risk of fetal ventricular arrhythmia events in HCM patients.	fQRS is significantly associated with heart failure with hospitalization and lower heart failure-free survival in HCM patient.	fQRS significantly increase risk of ventricular arrhythmias and SCD in HCM patients. fQRS is an independent high-risk indicator of SCD in HCM.

Note: ECG; electrocardiogram, fQRS; fragmented QRS, HCM; hypertrophic cardiomyopathy, ICD; implantable cardioverter defibrillator, IQR; Interquartile range, N/A; not applicable, SCD; sudden cardiac death, VF; ventricular fibrillation, VT; ventricular tachycardia