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Gender differences in prevalence and prognostic value of fragmented QRS complex

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ABSTRACT

Background: Fragmented QRS (fQRS) on 12-lead electrocardiogram (ECG) is associated with scarred myocardium and adverse outcome. However, the data on gender differences in terms of its prevalence and prognostic value is sparse. The aim of this study was to evaluate whether gender differences in fQRS exist among subjects drawn from populations with different risk profiles.

Methods: We analyzed fQRS from 12-lead ECG in 953 autopsy-confirmed victims of sudden cardiac death (SCD) (78% men; 67.0 ± 11.4 yrs), 1900 coronary artery disease (CAD) patients with angiographically confirmed stenosis of ≥50% (70% men; 66.6 ± 9.0 yrs, 43% with previous myocardial infarction [MI]), and in 10,904 adults drawn from the Finnish adult general population (52% men; 44.0 ± 8.5 yrs).

Results: Prevalence of fQRS was associated with older age, male sex and the history and severity of prior cardiac disease of subjects. Among the general population fQRS was more commonly found among men in comparison to women (20.5% vs. 14.8%, $p < 0.001$). The prevalence of fQRS rose gradually along with the severity of prior cardiac disease in both genders, yet remained significantly higher in the male population: subjects with suspected or known cardiac disease (25.4% vs. 15.8% $p < 0.001$), CAD patients without prior MI (39.9% vs. 26.4%, $p < 0.001$), CAD patients with prior MI (42.9% vs. 31.2%, $p < 0.001$), and victims of SCD (56.4% vs. 44.4%, $p < 0.001$).

Conclusions: The prevalence of QRS fragmentation varies in different populations. The fragmentation is clearly related to the underlying cardiac disease in both genders, however women seem to have significantly lower prevalence of fQRS in each patient population in comparison to men.

Introduction

The fragmentation of the QRS complex was first observed by Boineau and Cox in 1973 as a result of their experimentation with acute ischemia models in canines [1]. The QRS fragmentation (fQRS) is suggested to represent heterogeneous activation of the myocardium caused by either myocardial scarring or necrosis secondary to coronary artery disease (CAD) [2–4]. The scar tissue and the ischemic regions in the myocardium within the viable myocardial tissue cause a nonhomogenous activation by abnormal spatial and temporal impulse conduction which can induce notching and slurring of the QRS complex in the surface electrocardiogram (ECG) [5].

The presence of fQRS has been shown to correlate with a regional myocardial scar observed in single photon emission tomography among patients referred to nuclear stress test [6]. As a consequence, the fQRS in standard 12-lead ECG is considered as an indicator of myocardial scar in patients with CAD [4,7,8]. However, the fQRS is not specific marker for CAD as it is commonly seen in nonischemic cardiac diseases as well [9,10]. The conduction slowing or blocks due to myocardial damage, caused for example by inflammation or fibrosis, could be expressed as fQRS in the surface ECG [11].

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CD, cardiac disease; CI, confidence interval; ECG, electrocardiogram; fQRS, fragmented QRS complex; HR, hazard ratio; LVH, left ventricular hypertrophy; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; SCD, sudden cardiac death; SD, standard deviation; SPECT, single photon emission tomograph.

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Previously, the fQRS has been associated with various cardiac disorders and adverse outcomes in various patient populations [4]. Even though gender differences in numerous ECG abnormalities have been reported for cardiovascular disease and sudden cardiac death (SCD) [12–14], the gender-related differences of fQRS, in terms of its prevalence and prognostic value, have not been previously researched. Therefore, this study aims to explore these differences in three different patient populations with different risk profiles.

Methods

Patient populations

The subjects for this study were drawn from three different populations representing different cardiac risk profiles, ranging from low to high-risk subjects. The low- to moderate-risk subjects were drawn from the Coronary Heart Disease Study of the Finnish Mobile Clinic Health Examination Survey (further Mobile Clinic Health Examination Survey), which was conducted between 1966 and 1972 as part of a national population survey organized by the Finnish Social Insurance Institution. The original cohort consisted of 10,957 subjects aged between 30 and 59 years (52.3% men) who were drawn from different geographical regions of Finland at the time and represented the middle-aged Finnish population well. Each participant underwent a standard resting 12-lead ECG and examinations at the study baseline, as previously described [15]. Subjects with missing data or unreadable ECG were excluded. In addition, subjects with notched form of early repolarization were excluded in order to avoid overlapping between fQRS and early repolarization. Based on the use of cardiac medication, clinical history of previous myocardial infarction (MI), documented CAD, ECG signs of CAD (Minnesota codes: 1.1–1.3, 4.1–4.3, 5.1–5.2, 7.1 and 7.4) or congestive heart disease the subjects were divided into two groups for the current study: subjects without evident cardiac disease (N = 8220; 52.5% male) and subjects with known or suspected cardiac disease (N = 2044; 46.5% male).

The ARTEMIS study (Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection study, ClinicalTrials.gov identifier: NCT01426685) was a prospective observational study recruiting CAD patients with or without type 2 diabetes 3 to 6 months after coronary angiography. Subjects who met the guidelines criteria for prophylactic implantable cardioverter-defibrillator and who had life expectancy of ≤1 year due to comorbidity or left ventricular ejection fraction ≤35% were excluded from the study. After taking into consideration these exclusions, the study population included a total of 1946 CAD patients with significant stenosis (>50%) in at least 1 major epicardial artery. Of these subjects of the study total of 1900 had analyzable baseline resting 12-lead ECG available. Following, all the subjects of the study were divided into two groups for this study: subjects with previous MI (N = 904; 70.6% male) and subjects without any history of MI (N = 996; 66.0% male).

The FinGesture study (Finnish Genetic Study for Arrhythmic Events) had systematically collected clinical and autopsy data from victims of SCD in the region of Northern Finland between 1998 and 2017. Medico-legal autopsies were carried out for all of the 5869 victims of SCD at the Department of Forensics Medicine, University of Oulu, Oulu, Finland, and the National Institute for Health and Welfare, Oulu, Finland. The autopsies were performed by experienced forensic pathologists using contemporary guidelines for the purpose of diagnosing the cause of death. Premortem ECGs, recorded on average 2 years prior to the SCD, were available and analyzed in 1101 subjects (74.7% male). For this study only adult victims of SCD between ages of 30 and 80 years were selected for the analysis (N = 953; 77.9% male). More detailed methods of the FinGesture study have been reported earlier by Kaikkonen et al. [16].

Electrocardiography

Resting 12-lead ECGs were recorded with a paper speed of 50 mm/s and calibration of 1 mV per 10 mm. Two independent readers blinded to the outcome data graded the presence of fQRS in each ECG: Mobile Clinic Health Examination Survey (H.T. and J.T.T.), ARTEMIS (L.H. and T.V.K.) and FinGesture (L.H. and M.A.E.H.). The repeatability of the measurements was assessed by kappa values. Furthermore the Kappa values for the Mobile Clinic Health Examination Survey, ARTEMIS and the FinGesture studies were respectively 0.81, 0.79 and 0.63 for the presence of fQRS in any lead, respectively. Conflicting coding was resolved by consensus decision.

Fragmented QRS in subjects with normal QRS duration (<120 ms) was defined as an additional R wave (R′ or r′) or notching of the R or S wave in at least two contiguous leads in inferior (II, III, aVF), anterior (V1 to V3) or lateral (I, aVL, V4 to V6) leads (Fig. 1). Fragmented QRS in subjects with prolonged QRS duration due to e.g. paced rhythm or bundle branch block, was considered to be present if >2 notches, i.e. two additional notches, were observed in the R or S wave in at least two contiguous inferior, lateral or anterior leads (Fig. 2).

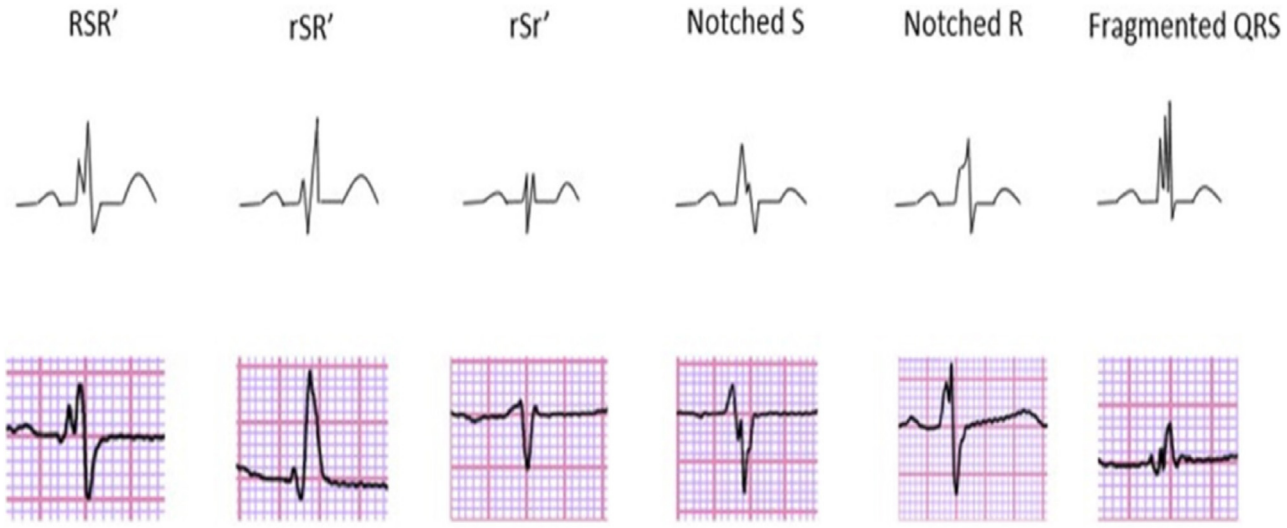

Fig. 1. An illustration of various fQRS morphologies on 12-lead ECG [19].
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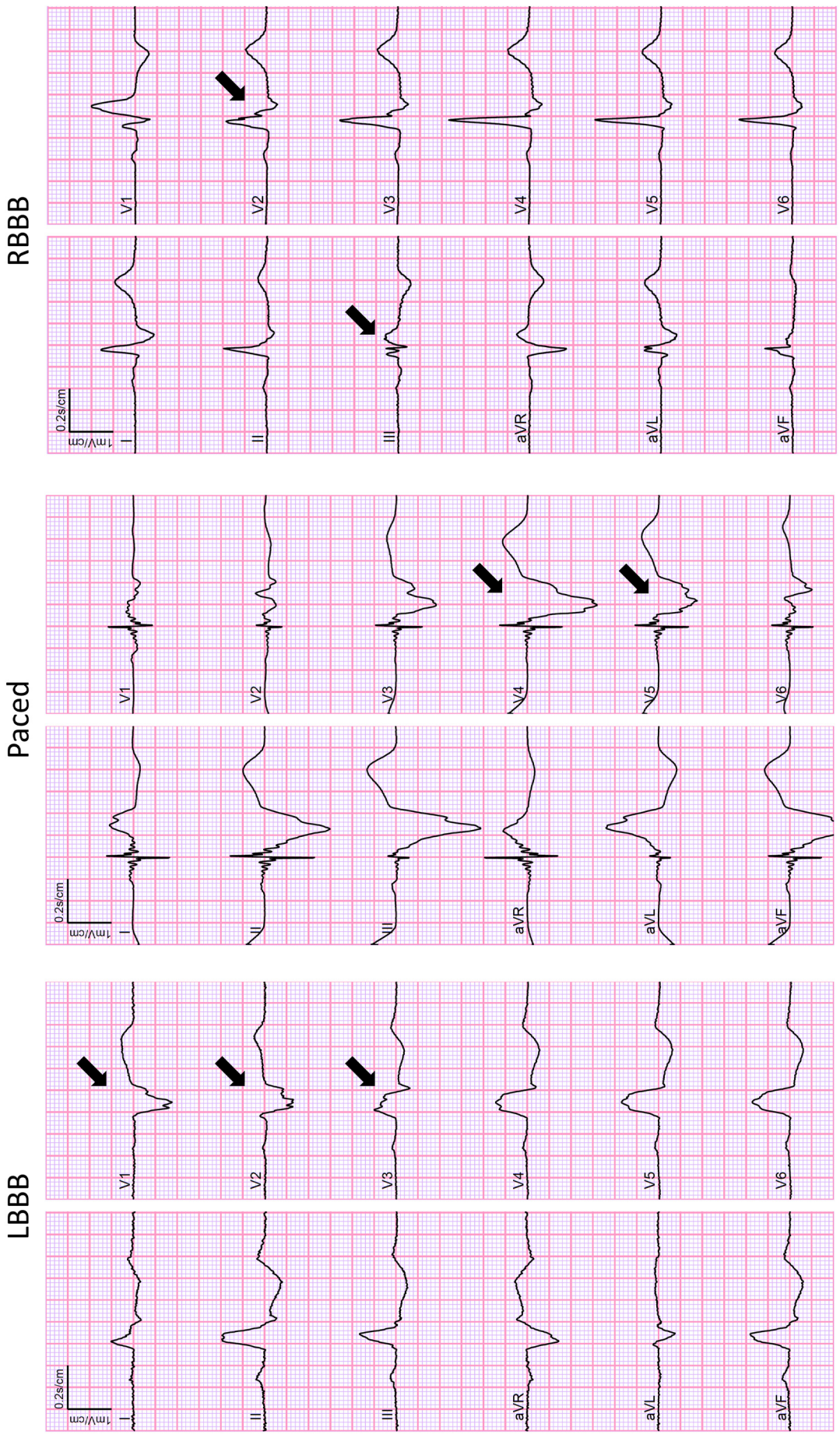

Fig. 2. Examples of fQRS in prolonged QRS complexes.

Sokolow-Lyon criteria was used for grading electrocardiographic left ventricular hypertrophy (LVH) i.e., if the sum of S wave amplitude in V1 and R wave amplitude in V5/V6 (whichever larger) was greater or equal to 35 mm, ECG was graded as positive for LVH. QRS duration and QT interval were measured from leads II or V5. Heart rate correction for the QT interval was performed with Bazett's formula.

Follow-up and endpoints

In the Coronary Heart Disease Study of the Finnish Mobile Clinic Health Examination Survey, the baseline measurements were performed between 1966 and 1972. The participants were followed-up for 30 ± 11 years until the end of year 2007. The primary endpoint was cardiac death and the secondary endpoints were sudden arrhythmic death and death from any cause. These causes of death were determined from death certificates provided by Statistics Finland. Furthermore, a committee of qualified and experienced cardiologists unaware of the ECG analysis reviewed all cardiac deaths by evaluating each case by using death certificates and hospital records. The details of study population have been described previously [15].

In the ARTEMIS study, the baseline measurements were performed between 2007 and 2011. The primary endpoint was cardiac death and the secondary endpoints were SCD and death from any cause. SCD was defined as witnessed death within 1 h from the onset of symptoms, or death without obvious extracardiac causes that occurred within 24 h the subject was last seen alive if the death was unwitnessed.

In the FinGesture study, death was classified as sudden if it was either a witnessed event within 6 h from the onset of symptoms or an unwitnessed death within 24 h when the subject was last seen alive in a normal state of health. If evidence of a noncardiac cause of the death was observed, subjects were excluded from the SCD cohort. Premortem ECGs were collected from all subjects with at least one ECG in their health records. The median time between the last available ECG prior to the SCD was 2 years (interquartile range: 0.28, 4.9 years).

All three studies were approved by the local ethics committees and followed the guidelines of The Declaration of Helsinki. In the Mobile Clinic Health Examination Survey and ARTEMIS study, written informed consent was given by the participants prior to the study. The Ethics Committee waived consent from the next of kin, as according to the Finnish law, medicolegal autopsy does not require consent.

Statistical analyses

All continuous variables are presented as mean ± standard deviation (SD) and categorical variables as number of cases with prevalence among the study population in brackets. General linear model was used to compare age- and gender-adjusted means for continuous variables. Pearson Chi-Square test was used to compare categorical

Table 1
Characteristics of study populations.

Variable		Finnish database (N = 10,957)				ARTEMIS (N = 1900)				FinGesture (N = 953)	
		No CD		Possible CD		Without MI		With MI		Female	Male
		Female	Male	Female	Male	Female	Male	Female	Male		
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
CAD, yes	fQRS-	0 (0.0%)	0 (0.0%)	96 (30.0%)	101 (23.9%)	248 (100.0%)	357 (100.0%)	183 (100.0%)	338 (100.0%)	98 (65.3%)	242 (66.3%)
	fQRS +	0 (0.0%)	0 (0.0%)	14 (23.0%)	29 (23.0%)	89 (100.0%)	244 (100.0%)	83 (100.0%)	258 (100.0%)	83 (64.3%)	298 (65.2%)
LVH, yes	fQRS -	779 (19.1%)	1755 (43.8%)	78 (27.2%)	181 (46.3%)	48 (19.4%)	38 (9.6%)	29 (15.8%)	26 (7.1%)	5 (3.3%)	21 (5.8%)
	fQRS +	143 (19.8%)	402 (37.3%)	19 (27.5%)	57 (24.2%)	25 (28.1%)	18 (6.9%)	22 (26.5%)	16 (5.8%)	7 (5.4%)	21 (4.6%)

Variable		Finnish database (N = 10,957)				ARTEMIS (N = 1900)				FinGesture (N = 953)	
		No CD		Possible CD		Without MI		With MI		Female	Male
		Female	Male	Female	Male	Female	Male	Female	Male		
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age, yrs	fQRS −	43.3 (8.2)	42.2 (8.1)	48.4 (8.1)	47.1 (8.5)	68.4 (7.7)	65.9 (7.5)	67.1 (8.5)	64.1 (8.5)	71.4 (12.4)	64.4 (11.8)
	fQRS +	44.4 (8.5)	42.4 (8.4)	49.9 (8.2)	49.2 (7.5)	68.6 (7.3)	65.8 (8.4)	69.6 (8.5)	64.0 (9.8)	70.6 (14.1)	64.0 (11.9)
BMI, kg/m^2	fQRS −	25.9 (4.2)	25.3 (3.2)	27.8 (5.0)	25.9 (3.8)	28.2 (5.2)	27.8 (3.8)	28.1 (4.4)	27.6 (4.2)	28.6 (8.6)	27.3 (8.6)
	fQRS +	26.6 (4.0)	26.0 (2.9)	28.6 (4.8)	26.1 (3.5)	28.3 (4.8)	28.5 (4.3)	29.4 (4.5)	28.4 (4.3)	28.4 (7.5)	27.6 (6.1)
HR, 1/min	fQRS −	79.2 (15.6)	71.6 (14.1)	80.1 (16.8)	73.8 (15.8)	61.5 (9.0)	58.4 (9.3)	60.5 (8.7)	59.6 (10.0)	78.8 (17.7)	78.1 (19.7)
	fQRS +	79.2 (15.8)	71.3 (14.7)	77.6 (16.1)	72.5 (15.3)	62.2 (10.0)	60.2 (10.0)	60.2 (10.0)	59.6 (10.5)	76.5 (16.8)	79.2 (18.6)
QRS duration, ms	fQRS −	82.3 (10.2)	85.3 (10.4)	83.1 (10.7)	87.2 (10.9)	95.8 (9.3)	101.4 (10.6)	94.6 (8.7)	100.7 (11.0)	89.6 (17.7)	95.5 (17.5)
	fQRS +	85.0 (10.4)	88.2 (10.8)	85.4 (9.9)	91.0 (10.3)	106.8 (23.5)	109.3 (22.4)	108.9 (22.4)	112.4 (21.7)	99.0 (26.7)	106.8 (25.2)
QTc interval, ms	fQRS −	413.5 (26.6)	400.1 (26.9)	418.9 (28.4)	408.1 (29.5)	425.1 (20.8)	415.5 (24.8)	425.7 (23.1)	417.2 (24.3)	432.7 (32.8)	432.3 (36.1)
	fQRS +	413.3 (26.5)	400.5 (27.6)	418.7 (28.3)	404.6 (31.0)	435.0 (23.7)	424.4 (26.5)	436.5 (30.3)	427.0 (29.0)	444.5 (42.0)	445.3 (47.1)

Values for subjects with fragmented QRS (fQRS) complex are presented below those for no QRS fragmentation. For categorical variables values are presented as number of cases within fQRS−/fQRS+ and corresponding percentage within brackets. Continuous values are presented as mean with standard deviation (SD) below to it. Underlined values differed statistically significantly ($p < 0.05$) between fQRS+ and fQRS− cases. BMI = body mass index; CAD = coronary artery disease; CD = cardiac disease; HR = heart rhythm; LVH = left ventricular hypertrophy; MI = myocardial infarction; SCD = sudden cardiac death.

variables between the groups. Cox proportional hazards model was used to calculate hazard ratios (HR) and their 95% confidence intervals (CI). In the multivariate model age, gender, BMI, cholesterol levels, smoking, systolic and diastolic blood pressure, QRS duration and QTc time were used as covariates. The proportional hazard assumption was verified for each risk marker by plotting Schoenfeld residuals against survival time transformed into natural logarithms. The statistical significance of gender interaction was tested by using the Wald test and all statistical analyses were performed by using Statistical Package for Social Studies version 25.0 (IBM SPSS Statistics). p value of <0.05 was considered statistically significant.

Results

The characteristics of study population and comparisons between subjects with and without fQRS by sex are shown in Tables 1 and 2. The prevalence of fQRS was associated with older age, male gender, and severity of prior cardiac disease. In the Mobile Clinic Health Examination Survey, a total of 6159 (56.5%) subjects passed away during the follow-up period (30 ± 11 years), of which 1981 (32.2%) were due to cardiac death and 802 (13.0%) due to sudden arrhythmic death. In the ARTEMIS study, a total of 212 (10.9%) passed or were resuscitated during the follow-up period (4.7 ± 0.8 years). Out of these 103 (5.3%) were due to cardiac death and 52 (2.7%) due to SCD.

Gender differences in the prevalence of fQRS

The prevalence of fQRS among subjects without clinical or electrocardiographic features of cardiac disease was 19.0%. The fragmentation was more frequent among men: 20.5% vs. 14.8%, p < 0.001. In 82.0% of the fQRS cases, fragmentation was observed in the inferior leads (men vs. women: 91.1% vs. 83.0%), whereas fragmentation in anterior and lateral leads was less frequent (15.1% and 2.9%). The gender differences in prevalence of fQRS in different populations are shown in Fig. 3.

Among subjects with known or suspected cardiac disease, the prevalence of fQRS was 22.3%, with significantly higher prevalence among men (25.4% vs. 15.8%, p < 0.001). Majority (74.8%) of fragmentation was observed in inferior leads (men vs. women: 82.6% vs. 85.3%).

In the ARTEMIS study, among subjects with angiographically documented CAD with ≥50% occlusion in one of the main coronary arteries without prior myocardial infarction, fragmentation was observed in 35.3% of cases. Men had significantly higher prevalence of fQRS than women: 39.9% vs. 26.4%, p < 0.001. The majority of fragmentations were observed in inferior leads.

If prior myocardial infarction had occurred, the prevalence of fQRS rose to 39.5%, with 42.9% of men and 31.2% of women displaying fragmented QRS complexes in their ECG recordings (p < 0.001). Majority of fQRS was observed in inferior leads.

Among victims of SCD, the overall prevalence of fQRS was the highest (53.8%) and where men had more often fQRS than women: 56.1% vs. 46.0%, p = 0.009. Majority of fragmentation was observed in inferior leads (79.3%), following in lateral (47.0%) and anterior (36.3%) leads. Men had statistically significantly more inferior fragmentation than women: 44.6% vs. 36.0%, p = 0.026. Histological samples were collected from the myocardium in all victims of SCD in the FinGesture study. A gradual increase in the prevalence of fQRS was observed with increasing degree of myocardial fibrosis (Fig. 4).

Gender differences in the prognostic value of fQRS

Men had overall higher mortality rates than women among subjects with QRS fragmentation with respect to sudden arrhythmic death (8.1% vs. 4.4%), cardiac death (18.4% vs. 13.7%) and total mortality (57.5% vs. 47.6%) during the 30-year follow-up. In women total and inferior fQRS was associated with slightly increased risk for cardiac death and all-cause mortality but statistical significance was not retained after multivariable analysis (Table 3). Gender interactions could be seen only in subjects without a previous cardiac disease for inferior and total fQRS (Table 4).

Table 2
Sex differences in the characteristics.

Variable	Finnish database (N = 10,957)				ARTEMIS (N = 1900)				FinGesture (N = 953)	
	No CD		Possible CD		Without MI		With MI		Female (211)	Male (742)
	Female (3904)	Male (4316)	Female (1094)	Male (950)	Female (339)	Male (657)	Female (266)	Male (638)		
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
CAD, yes	0 (0.0%)	0 (0.0%)	110 (10.1%)	130 (13.7%)	339 (100.0%)	657 (100.0%)	266 (100.0%)	638 (100.0%)	104 (49.2%)	456 (61.5%)
LVH, yes	938 (24.0%)	2190 (50.7%)	86 (7.9%)	252 (26.5%)	73 (21.5%)	56 (8.5%)	51 (19.2%)	42 (6.6%)	12 (5.7%)	42 (5.7%)
fQRS, yes	578 (14.8%)	906 (21.0%)	173 (15.8%)	241 (25.4%)	89 (26.4%)	262 (39.9%)	83 (31.2%)	274 (42.9%)	97 (46.0%)	416 (56.1%)

Variable	Finnish database (N = 10,957)				ARTEMIS (N = 1900)				FinGesture (N = 953)	
	No CD		Possible CD		Without MI		With MI			
	Female (3904)	Male (4316)	Female (1094)	Male (950)	Female (339)	Male (657)	Female (266)	Male (638)	Female (211)	Male (742)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age, yrs.	43.8 (8.3)	43.0 (8.3)	51.4 (7.0)	50.5 (7.0)	69.1 (7.7)	66.6 (8.1)	68.7 (8.4)	65.2 (9.3)	70.1 (13.1)	63.5 (11.8)
BMI, kg/m^2	26.1 (4.3)	25.6 (3.2)	27.9 (5.0)	26.0 (3.7)	28.5 (5.3)	28.2 (4.2)	28.7 (4.7)	28.2 (4.5)	28.3 (7.6)	27.5 (6.0)
HR, 1/min	79.6 (15.5)	71.9 (14.1)	78.7 (16.2)	72.7 (15.3)	67.8 (8.4)	68.0 (9.3)	66.5 (8.8)	67.5 (9.3)	77.7 (17.3)	78.7 (19.1)
QRS duration, ms	85.0 (7.7)	88.7 (8.6)	86.0 (9.1)	109.3 (11.1)	100.2 (16.8)	105.1 (17.6)	99.1 (16.2)	106.5 (18.2)	93.9 (22.8)	101.8 (22.8)
QTc interval, ms	415.1 (26.2)	401.4 (26.8)	417.0 (27.8)	406.5 (29.8)	428.3 (23.3)	421.7 (26.7)	430.2 (26.1)	423.2 (27.7)	438.2 (37.7)	439.5 (39.8)

For categorical variables values are presented as number of cases within sex and corresponding percentage within brackets. Continuous values are presented as mean with standard deviation (SD) below to it. Underlined values differed statistically significantly (p < 0.05) between female and male subjects. BMI = body mass index; CAD = coronary artery disease; CD = cardiac disease; HR = heart rhythm; LVH = left ventricular hypertrophy; MI = myocardial infarction; SCD = sudden cardiac death.

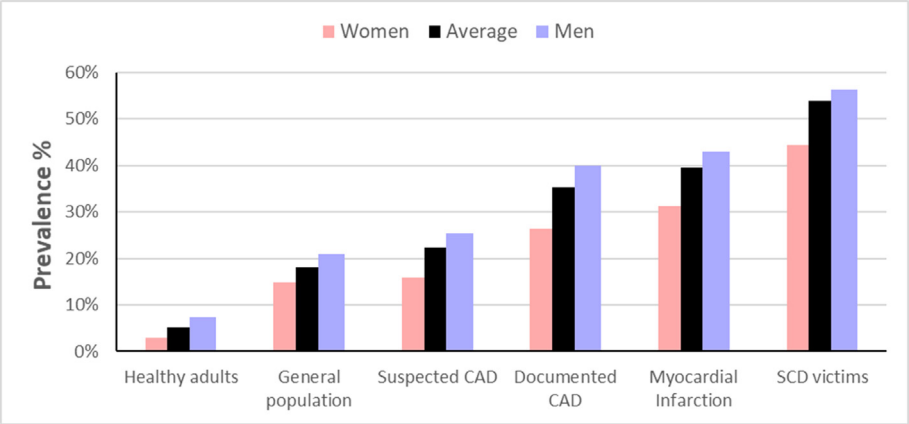

Fig. 3. The prevalence of the QRS fragmentation in the different populations.

In the presence of known or suspected cardiac disease, fQRS in any leads increased only slightly the risk for cardiac mortality in multivariable model (Table 3). However, lateral fQRS was associated with increased risk for arrhythmic, cardiac and all-cause mortality when adjusted with age, sex, BMI, cholesterol levels, smoking, systolic blood pressure, QRS duration and QTc time (Table 3). In women prognostic significance was not obtained for fQRS in any leads (Table 3), but in men fQRS in any two contiguous leads increased risk for cardiac death. Again, lateral fQRS in male subjects with a known cardiac disease increased risk for arrhythmic death 4.0-folded and risk of death in any cause 2.6-folded in multivariable model (Table 3). However, any gender interactions could not be detected in subjects with a known cardiac disease (Table 4).

Discussion

The study explored gender differences in the prevalence and prognostic value of fQRS in three different populations covering different cardiac risk profiles. To our knowledge, the study is the first to assess these differences. However, gender differences in the prevalence and prognostic value of other ECG abnormalities have been reported in earlier literature, see for example ECG sign of LVH associated with SCD [14] and greater risk for cardiovascular mortality especially among women [17], and prolonged QTc time has been reported to associate with a future coronary event only in women [18]. In the study it was discovered that the prevalence of fQRS is associated with older age, male gender and increased overall risk of the subjects. A near linear trend in the prevalence of fQRS was found among both men and women, with significantly higher occurrence among subjects with more advanced cardiac disease. Though the relationship was evident in both genders, the prevalence of fQRS was higher among men in each population of the study. Further analyses on histological samples collected from the victims of SCD (FinGesture) presented a clear association between elevated degrees of myocardial fibrosis and prevalence of fQRS.

Gender differences in the prevalence of fragmented QRS

Based on the findings the prevalence of fQRS seems to be the higher the unhealthier the population is regardless of the gender. The prevalence of fQRS rose consistently from general population (19.0%) to patients with suspected CAD (22.3%) continuing rising from documented CAD (35.3%) to myocardial infarction (39.5%) being the highest among victims of SCD (53.8%) (Fig. 3). Previous data can be found describing similar kind of process. The prevalence in a healthy adult population is described to be approximately 5% [10]. In the general population, fQRS is observed in 19.0% of subjects with no clinical or electrocardiographic evidence of cardiac disease [19]. As well, fQRS can be observed in approximately 20–35% of the subjects with known or suspected CAD [6]. In patients with non-ST elevation myocardial infarction (NSTEMI) fQRS was considerably more prevalent (51%) compared patients with unstable angina pectoris (3.7%) [20].

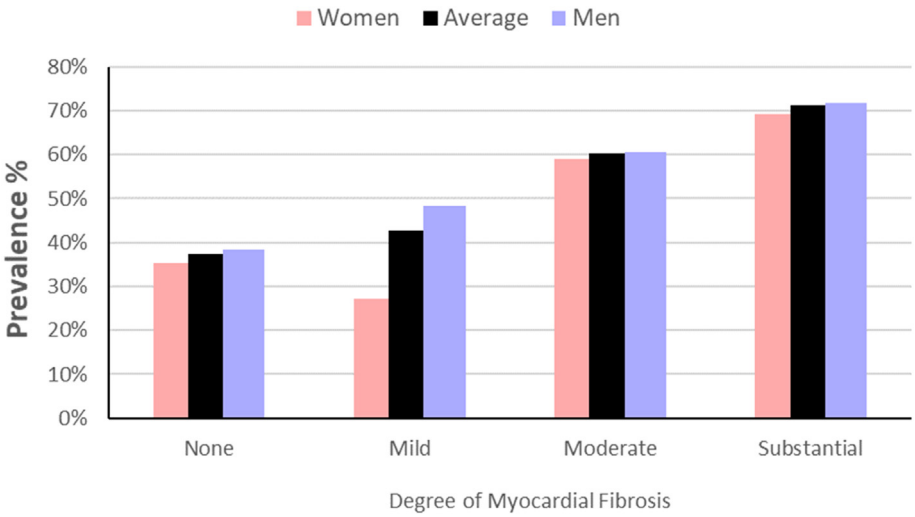

Fig. 4. The prevalence of the QRS fragmentation with respect to histological samples from autopsy data among the victims of sudden cardiac death.

Table 3
Unadjusted and adjusted relative risks of death for subjects with and without a known cardiac disease.

	Subjects without a known cardiac disease (N = 8220)						Subjects with a known cardiac disease (N = 2044)					
	N.o. of deaths (%)		Univariate HR (95% CI)		Multivariate HR (95% CI)		N.o. of deaths (%)		Univariate HR (95% CI)		Multivariate HR (95% CI)	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Cardiac death												
Total fQRS	111 (19%)	207 (19%)	1.4 (1.13–1.71)	0.9 (0.79–1.08)	1.2 (0.96–1.46)	0.9 (0.73–0.99)	15 (23%)	63 (49%)	1.0 (0.56–1.71)	1.4 (1.02–1.85)	0.95 (0.54–1.68)	1.6 (1.16–2.12)
Inferior fQRS	97 (16%)	185 (19%)	1.5 (1.18–1.83)	0.9 (0.78–1.07)	1.2 (0.95–1.47)	0.8 (0.71–0.98)	13 (25%)	45 (46%)	1.1 (0.58–1.91)	1.2 (0.89–1.74)	1.0 (0.55–1.86)	1.4 (1.02–2.03)
Anterior fQRS	14 (11%)	30 (20%)	0.9 (0.53–1.54)	1.0 (0.71–1.48)	1.0 (0.59–1.72)	1.0 (0.69–1.45)	2 (17%)	17 (63%)	0.7 (0.17–2.74)	1.9 (1.15–3.14)	0.7 (0.1–2.71)	1.8 (1.04–3.09)
Lateral fQRS	5 (18%)	6 (16%)	1.8 (0.73–4.23)	0.85 (0.38–1.89)	1.3 (0.55–3.27)	1.1 (0.49–2.47)	0 (0%)	10 (67%)	0.05 (0.00-[)	3.0 (1.56–5.64)	0.0 (0.00-[)	4.3 (2.20–8.33)
Arrhythmic death												
Total fQRS	34 (4.8%)	106 (9.9%)	1.2 (0.86–1.80)	1.0 (0.81–1.24)	1.1 (0.79–1.66)	0.9 (0.76–1.17)	2 (3.1%)	27 (21%)	0.5 (0.11–2.06)	1.3 (0.85–2.08)	0.4 (0.10–1.89)	1.5 (0.94–2.36)
Inferior fQRS	31 (5.2%)	95 (9.8%)	1.4 (0.93–2.01)	1.0 (0.79–1.24)	1.2 (0.81–1.77)	0.9 (0.74–1.16)	1 (1.9%)	18 (18%)	0.3 (0.04–2.23)	1.1 (0.67–1.91)	0.3 (0.04–1.98)	1.3 (0.76–2.20)
Anterior fQRS	4 (3.1%)	14 (9.5%)	0.8 (0.29–2.07)	1.0 (0.59–1.71)	0.9 (0.32–2.36)	1.0 (0.55–1.66)	1 (8.3%)	7 (26%)	1.2 (0.15–8.60)	1.7 (0.78–3.71)	1.2 (0.16–9.22)	1.6 (0.67–3.68)
Lateral fQRS	4 (3.1%)	2 (5.3%)	1.0 (0.14–7.27)	0.6 (0.15–2.39)	0.8 (0.11–5.40	0.8 (0.19–3.07)	0 (0%)	6 (40.0%)	0.05 (0.00-[)	3.9 (1.68–8.96)	0.0 (0.00-[)	5.0 (2.10–12.0)
All-cause mortality												
Total fQRS	366 (51%)	644 (60%)	1.2 (1.08–1.36)	1.0 (0.89–1.05)	1.0 (0.92–1.16)	0.9 (0.84–1.00)	50 (78%)	114 (88%)	1.0 (0.77–1.42)	1.1 (0.86–1.31)	1.0 (0.71–1.34)	1.2 (0.95–1.47)
Inferior fQRS	312 (52%)	575 (60%)	1.3 (1.11–1.41)	0.95 (0.87–1.04)	1.0 (0.90–1.15)	0.9 (0.82–0.99)	41 (79%)	86 (87%)	1.1 (0.76–1.48)	1.0 (0.80–1.29)	1.0 (0.68–1.35)	1.1 (0.89–1.44)
Anterior fQRS	60 (46%)	94 (64%)	1.0 (0.80–1.34)	1.1 (0.89–1.34)	1.1 (0.85–1.43)	1.0 (0.83–1.26)	9 (75%)	25 (93%)	1.0 (0.49–1.86)	1.2 (0.83–1.86)	0.9 (0.45–1.74)	1.2 (0.79–1.88)
Lateral fQRS	17 (61%)	22 (58%)	1.6 (0.97–2.53)	1.0 (0.69–1.59)	1.2 (0.73–1.97)	1.2 (0.80–1.89)	1 (33%)	14 (93%)	0.3 (0.04–2.11)	1.8 (1.05–3.07)	1.0 (0.13–7.14)	2.6 (1.52–4.56)

Statistical analysis was made for subjects of Coronary Heart Disease Study of the Finnish Mobile Clinic Health Examination Survey. Results are adjusted with age, sex, BMI, cholesterol levels, smoking, systolic blood pressure, QRS duration and QTc time. Statistically significant values ($p < 0.05$) are underlined. CI = confidence interval; HR = hazard ratio.

However, women seem to have significantly lower prevalence of fQRS in each patient population compared to men. Altogether, the same increasing trend in the prevalence of fQRS could be seen in women as well as in men (Fig. 3). Male subjects had fQRS more often compared to women among subjects with no apparent cardiac disease. This difference can be largely explained by more frequent fragmentation of the inferior leads among men (19.0% vs. 12.6%). The same trend repeated in subjects with known or suspected cardiac disease. Among the victims of SCD the prevalence of fQRS was significantly higher among men (56.4%) than in women (44.4%). The findings of the study are in line with some previous studies in general population and subjects with evidence of cardiac disease [19]as well as patients with NSTEMI [26]. However, the comparison of prevalence difference between the genders in previous literature is rare so the novelty value of the findings cannot be passed.

Association between fibrosis and fQRS

Interestingly, gradual increase in prevalence of QRS fragmentation was found when combined with the increase in amount of myocardial fibrosis when analyzing the histological samples of victims of SCD. The prevalence of fQRS was slightly higher among men compared to women regardless of the degree of fibrosis. However, the greatest prevalence difference between the genders was detected with mild myocardial fibrosis. The gradual increase in the degree of fibrosis continued among men. However, in women the prevalence of fQRS was higher among subjects without fibrosis compared to those with higher degree of fibrosis.

This finding supports the thought that fQRS represents a local conduction slowing in the ventricular myocardium caused by either scar, fibrosis, inflammation or ischemia [11]. Approximately 70% of the SCDs

Table 4
Risk of death and gender interactions.

	Women vs. men							
	Total fQRS		Inferior fQRS		Anterior fQRS		Lateral fQRS	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Subjects without a known cardiac disease								
Cardiac death	1.5 (1.15–1.92)	0.003	1.6 (1.21–2.08)	0.001	0.9 (0.46–1.68)	0.696	2.0 (0.61–6.59)	0.254
Arrhythmic death	1.2 (0.80–1.89)	0.343	1.4 (0.88–2.13)	0.167	0.8 (0.25–2.34)	0.630	1.7 (0.15–18.37)	0.682
Death by any cause	1.2 (1.08–1.43)	0.002	1.3 (1.12–1.52)	0.001	0.9 (0.68–1.31)	0.723	1.5 (0.78–2.78)	0.233
Subjects with a known cardiac disease								
Cardiac death	0.7 (0.38–1.35)	0.303	0.9 (0.43–1.68)	0.647	0.3 (0.08–1.53)	0.162	0.0 (0.00-[)	0.900
Arrhythmic death	0.3 (0.08–1.60)	0.174	0.3 (0.03–2.05)	0.199	0.7 (0.08–5.70)	0.707	0.0 (0.00-[)	0.922
Death by any cause	1.0 (0.69–1.45)	0.999	1.1 (0.71–1.61)	0.752	0.77(0.35–1.67)	0.504	0.2 (0.02–1.31)	0.089

Statistical analysis was made for subjects of Coronary Heart Disease Study of the Finnish Mobile Clinic Health Examination Survey. Interactions between gender and fQRS were assessed using Cox regression analysis. Statistically significant interactions ($p < 0.05$) are underlined. CI = confidence interval; HR = hazard ratio.

are ischemic etiology [27, 28]. The presence of fQRS has been previously proved by single photon emission tomography (SPECT) to be 4–6-times higher in patients with ischemia and infarction compared with the control group [29], and to have greater correlation to a regional myocardial scar and significantly greater sensitivity in detection of myocardial scar is significantly greater (85.6%) than the Q wave has (36.3%) [6]. In patients with ST elevation myocardial infarction fQRS correlates with larger infarct size and peri-infarct zone as well as poorer acute ventricular remodeling [7]. The highest accuracy for myocardial fibrosis has been showed in fQRS in lateral leads [30].

Gender differences in the prognostic value of fQRS

Among subjects with no evidence of cardiac disease, fQRS was not predictive of arrhythmic, cardiac or all-cause mortality during a long-term follow-up [19]. However, among patients with suspected or known cardiac disease it was found out that lateral fQRS associated 3-folded risk for arrhythmic death (HR: 3.0, CI: 1.43–6.56, $p < 0.001$), 2.5-folded risk for cardiac death (HR: 2.5, CI: 1.45–4.22, $p < 0.001$) and almost 2-folded risk for all-cause mortality (HR:1.9, CI: 1.27–2.70, $p < 0.001$). In previous studies fragmented QRS complex has been associated with adverse outcome in several studies from different patient populations [4]. These findings support the concept that isolated fQRS in the absence of known or suspected cardiac disease is not a specific marker of increased risk of mortality.

In the current study male subjects with QRS fragmentation had overall higher mortality rates compared to women, but interaction between sex was noticed only in patients without a previous cardiac disease for inferior and total fQRS. Prognostic value for fQRS was significant only in male subjects with a previous cardiac disease. Literature on the sex differences in the prognostic value of fQRS is sparse. Part of the reason might be lower prevalence of fQRS among women and lower incidence of adverse outcomes.

Limitations

Unfortunately, the proportion of female subjects in the study populations is the lower the unhealthier the population is due to the fact that cardiac illnesses are more common among men. This may, however, produce some bias to the study. In addition, pre-mortem ECG's were able to be obtained in only one of the fifth of the subjects of our SCD population.

Conclusions

The present study is the first of its kind to examine the gender differences in prevalence and prognosis of fQRS. Prevalence of fQRS varies depending on population. There is a clear relation between fQRS and the underlying cardiac disease in both genders which is indicated by the gradually increasing prevalence of fQRS and the risk accumulation of the population. However, women seem to have significantly lower prevalence of fQRS in each patient population compared to men. Despite the significant prevalence difference in the general population, gender interaction in the prognostic value of fQRS was seen only in subjects without a known cardiac disease. Interestingly, gradual increase in the prevalence of fQRS was observed with increasing degree of myocardial fibrosis in histological samples.

CRediT authorship contribution statement

M. Anette E. Haukilahti: Data curation, Formal analysis, Funding acquisition, Investigation, Writing - original draft, Writing - review & editing. **Lauri Holmström:** Data curation, Writing - review & editing. **Juha Vähätalo:** Data curation, Writing - review & editing. **Jani T. Tikkanen:** Data curation, Writing - review & editing. **Henri K. Terho:** Data curation, Investigation, Writing - review & editing. **Antti M. Kiviniemi:** Data curation, Methodology, Writing - review & editing. **E. Samuli Lepojärvi:** Data curation, Writing - review & editing. **Mikko Tulppo:** Data curation, Writing - review & editing. **Juha S. Perkiömäki:** Data curation, Writing - review & editing. **Olavi H. Ukkola:** Data curation, Writing - review & editing. **Olli Anttonen:** Data curation, Writing - review & editing. **Aapo L. Aro:** Data curation, Writing - review & editing. **Tuomas Kerola:** Data curation, Writing - review & editing. **Harri Rissanen:** Data curation, Writing - review & editing. **Paul Knekt:** Data curation, Writing - review & editing. **M. Juhani Junttila:** Conceptualization, Data curation, Funding acquisition, Project administration, Supervision, Writing - review & editing. **Heikki V. Huikuri:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing. **Tuomas V. Kenttä:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing - review & editing.

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