

# QRS Fragmentation and Sudden Cardiac Death in the Obese and Overweight

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**Background**—Obesity has been associated with significantly greater risk of sudden cardiac death (SCD); however, identifying the obese patient at highest risk remains a challenge. We evaluated the association between QRS fragmentation on the 12-lead electrocardiogram and SCD, in obese/overweight subjects.

**Methods and Results**—In the ongoing prospective, community-based Oregon Sudden Unexpected Death Study (population approximately 1 million), we performed a case-control analysis, comparing obese/overweight SCD victims with obese/overweight controls from the same geographic region. Archived ECGs prior and unrelated to the SCD event were used for cases and all ECG measurements were assessed in blinded fashion. Fragmentation was defined as the presence of RSR' patterns and/or notching of the R/S wave in at least 2 contiguous leads. Analysis was limited to ECGs with QRS duration <120 ms. Overall prevalence of fragmentation was higher in cases (n=185; 64.9±13.8 years; 67.0% male) compared with controls (n=405; 64.9±11.0 years; 64.7% male) (34.6% versus 26.9%,  $P=0.06$ ). Lateral fragmentation was significantly more frequent in cases (8.1% versus 2.5%;  $P<0.01$ ), with non-significant differences in anterior and inferior territories. Fragmentation in multiple territories ( $\geq 2$ ) was also more likely to be observed in cases (9.7% versus 4.9%,  $P=0.02$ ). In multivariable analysis with consideration of established SCD risk factors, lateral fragmentation was significantly associated with SCD (OR 2.84; 95% CI 1.01 to 8.02;  $P=0.05$ ).

**Conclusion**—QRS fragmentation, especially in the lateral territory is a potential risk marker for SCD independent of the ejection fraction, among obese/overweight subjects in the general population. (*J Am Heart Assoc.* 2015;4:e001654 doi: 10.1161/JAHA.114.001654)

**Key Words:** ECG • obesity • QRS fragmentation • sudden cardiac death

Current estimates suggest that more than one-third of the world population is overweight or obese. In the United States, with more than two-thirds of the adult population overweight and one-third obese, obesity has been upgraded from a “condition” to a “disease.”<sup>1,2</sup> Obesity is closely associated with the metabolic syndrome<sup>3</sup> and has been linked to adverse cardiovascular prognosis and mortality.<sup>4,5</sup> A diagno-

sis of obesity predicts incident coronary artery disease (CAD) over and above the traditional coronary risk factors and has been reported to be additive to the Framingham risk score.<sup>6</sup>

Large cohort studies<sup>7,8</sup> as well as population-based analysis from the Oregon Sudden Unexpected Death Study (SUDS)<sup>9</sup> have confirmed obesity/overweight as a risk factor for sudden cardiac death (SCD). The link between obesity and arrhythmia is likely multifactorial and continues to be an area of active research. Of particular interest is the adverse cardiac remodeling associated with obesity. Obesity has been linked to left atrial and ventricular dilatation<sup>10</sup> as well as left ventricular hypertrophy and diastolic dysfunction.<sup>11,12</sup> Recent animal<sup>13</sup> as well as clinical<sup>14</sup> studies have suggested that fatty infiltration of the myocardium may itself predispose to ventricular arrhythmia, potentially as a result of poor electrical conductivity of fat which could favor delayed impulse transmission and re-entry.

Electrical disturbances arising as a result of fatty infiltration/fibrosis may thus represent an important mechanism of arrhythmogenesis in obesity. QRS fragmentation (fQRS) on the surface ECG has been reported to be a surrogate marker of inhomogeneous conduction and delayed activation in the

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myocardium.<sup>15</sup> Fragmented QRS complexes, thought to reflect myocardial scarring, have been linked to adverse cardiac prognosis as well as cardiac mortality.<sup>16,17</sup> Moreover, earlier studies have suggested that QRS fragmentation predicts risk of arrhythmia in a variety of cardiac conditions.<sup>18–21</sup>

However, a potential association between QRS fragmentation and SCD in the general population needs further evaluation. It would be of significant interest to assess whether this simple, non-invasive marker on the surface ECG could help identify high-risk sub-groups within the obese/overweight population. In light of the available knowledge about the pathophysiology of obesity and SCD, especially with regard to the effect of obesity on cardiac structure, we postulated that QRS fragmentation may be a useful marker to identify those at risk of SCD among obese/overweight subjects in the community. We therefore undertook a systematic investigation of the potential utility of QRS fragmentation, among obese/overweight subjects in the general population.

## Methods

### Study Population and Definitions

This is a community-based, observational, case-control study. The Oregon SUDS is a prospective, population-based study of out-of-hospital SCD. Detailed methods and descriptions have been published earlier.<sup>22–24</sup> Briefly, cases of possible SCD are prospectively ascertained in the Portland, Oregon metropolitan area (population approximately 1 million) using multiple sources, which include first responders, local hospital emergency rooms, and the county medical examiner. After detailed review of available medical records, autopsy reports, and the circumstances of arrest, SCD cases are identified through a 3-physician adjudication system. SCD is defined as an unexpected sudden, pulseless condition of cardiac etiology, occurring within 1 hour of symptom onset in witnessed cases and within 24 hours if unwitnessed. Survivors of sudden cardiac arrest are also included as SCD cases. Subjects with known terminal illnesses (such as cancer), non-cardiac causes of sudden death (such as cerebrovascular accident), and drug overdose are excluded. In parallel, controls are recruited from the same geographical location. Controls are subjects with no history of cardiac arrest, and are chosen to achieve a mix of a majority of subjects with coronary artery disease (CAD) and a minority of healthy controls from the population. The study is designed for the majority of controls (80%) to have CAD since published studies have established that a similar majority of SCD cases in the community have associated CAD.<sup>25</sup> CAD was defined as  $\geq 50\%$  stenosis in a major coronary artery. CAD controls are recruited from among subjects undergoing angiography at one of the region's major participating health

systems, those who were transported by the emergency medical system (EMS) for symptoms of acute coronary ischemia or subjects with diagnosed CAD from the region's Kaiser Permanente system. SCD cases  $\geq 50$  years of age were assumed to have CAD based on  $>95\%$  likelihood of CAD in such cases.<sup>26</sup> Detailed demographic and clinical information was collected for cases and controls from available medical records. Left ventricular (LV) function was evaluated by measurement of the LV ejection fraction (EF) and categorized as normal LV function ( $\geq 55\%$ ), mild to moderate dysfunction (36–54%), or severe dysfunction ( $\leq 35\%$ ). Body mass index (BMI) was calculated for subjects using weight and height measurements. As per National Institute of Health Guidelines, overweight was defined as a BMI of 25 to 29.9 kg/m<sup>2</sup>, and obesity was defined as a BMI of  $\geq 30$  kg/m<sup>2</sup>.<sup>27</sup> The present study compared obese/overweight SCD cases with obese/overweight controls from the same geographical area. Other than being from the same geographic location, no other specific matching was performed between cases and controls.

### QRS Fragmentation and Other ECG Parameters

Parameters assessed from the 12-lead ECG included heart rate, QRS duration, QT interval, presence of Q waves, and QRS fragmentation. ECGs prior but unrelated to the SCD event were used for cases. Taking into consideration previously established criteria for assessing fQRS,<sup>15</sup> the present analysis was limited to ECGs with narrow QRS (QRS duration  $< 120$  ms). The QT interval was corrected using Bazett's formula<sup>28</sup> and categorized as normal or abnormal using sex-specific criteria (men: QT c  $\leq 430$  ms—normal, 431 to 450 ms—borderline,  $> 450$  ms—abnormal; women: QTc  $\leq 450$  ms—normal, 451 to 470 ms—borderline,  $> 470$  ms—abnormal).<sup>29</sup> Pathologic Q waves were defined as Q waves  $\geq 40$  milliseconds in duration and  $> 25\%$  of the voltage of the following R wave. Q waves were classified according to territory, based on presence in at least 2 contiguous leads, as anterior (leads V1–V5), lateral (leads I, aVL, and V6), and inferior (leads II, III, and aVF). fQRS was identified as previously defined<sup>15</sup> by the presence of various RSR' patterns with or without Q wave, including an additional R wave (R'), notching of the R wave, notching in the nadir of the S wave, or the presence of more than 1 R' (fragmentation) in at least 2 contiguous leads corresponding to a major coronary artery territory (Figure 1A and 1B). If notching was confined only to the terminal QRS accompanied by J point elevation of  $\geq 0.1$  mV, it was classified as early repolarization pattern rather than fragmentation. Fragmentation was classified by anatomic territory, similar to Q waves, into anterior (leads V1–V5), lateral (leads I, aVL, and V6), or inferior (leads II, III, and aVF). ECG assessment for fragmentation and Q waves were performed by 2 trained readers blinded to the case/control

status of the subjects. The study was approved by the Institutional Review Boards of Cedars-Sinai Medical Center, Oregon Health and Science University, and all participating hospitals.

## Statistical Analysis

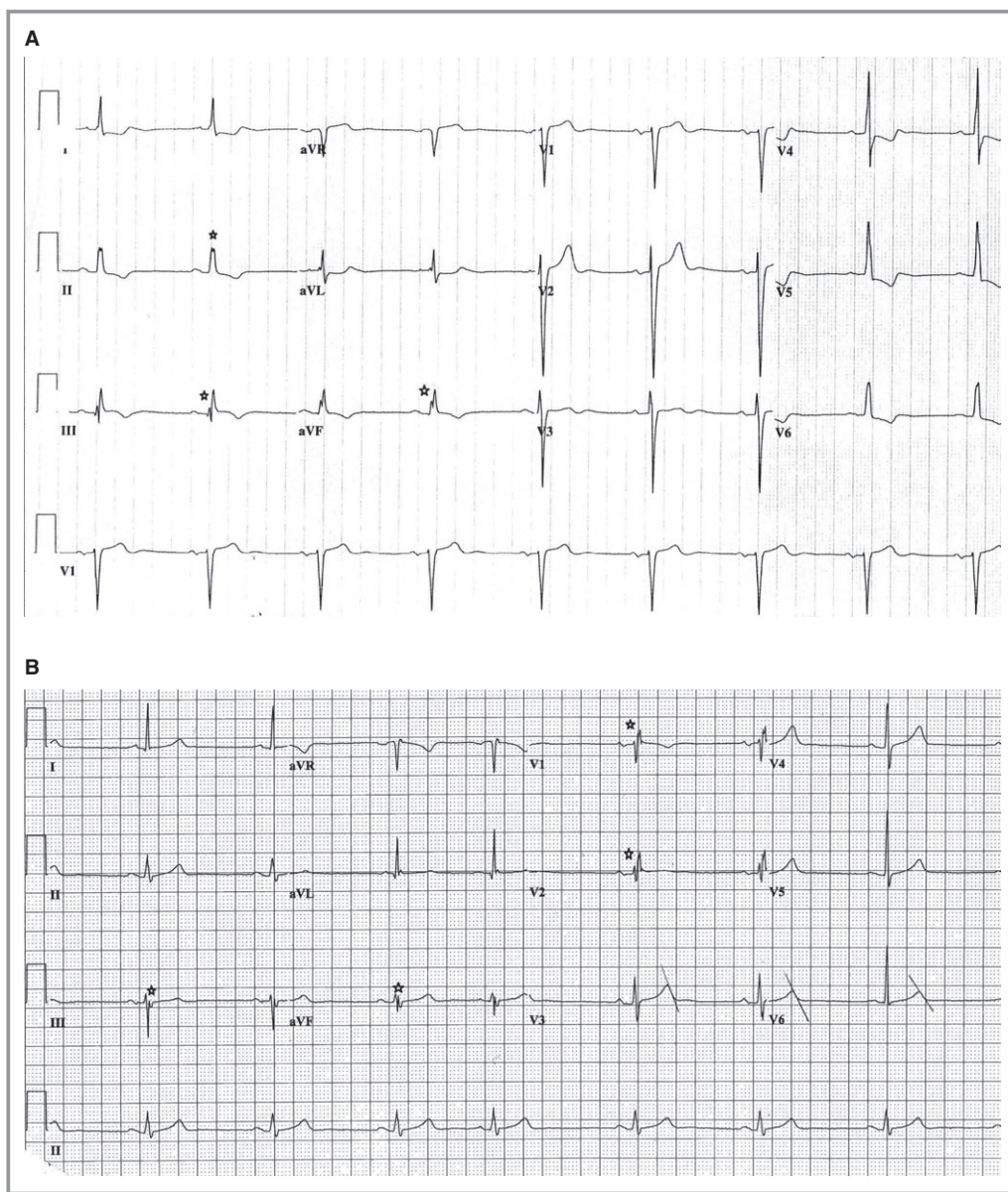
Student *t* tests and Pearson's  $\chi^2$  tests were used for comparisons of continuous variables (presented as mean $\pm$ standard deviation) and categorical variables (presented as numbers and percentages), respectively. Multivariable logistic regression was used to estimate odds ratios (OR) for the association of fQRS with SCD case status after adjusting for parameters that were significant in the univariate

analyses. For the multivariable model, QTc (as described earlier) and heart rate ( $\geq 100$  versus  $< 100$  bpm) were categorized based on accepted standards. Results were reported as 2-tailed *P* values, with a *P* value of  $\leq 0.05$  being considered statistically significant. All analyses were performed using SPSS statistical software (version 20.0 for Windows, SPSS Inc, IBM Corporation, New York).

## Results

### Demographic and Clinical Characteristics

A total of 590 obese/overweight subjects (185 cases and 405 controls) were studied. Demographic and clinical



**Figure 1.** Examples of ECGs showing fragmentation. A, 12-lead ECG with inferior fragmentation. B, 12-lead ECG with anterior and inferior fragmentation. ECG indicates electrocardiogram.



characteristics of cases and controls are shown in Table 1. Age, sex, frequency of current/former smokers, and the relative proportions of overweight and obese were not significantly different between case and control groups. Severe LV dysfunction (LVEF  $\leq$ 35%; 14.6% versus 4.7%;  $P<0.01$ ), diabetes mellitus (43.8% versus 29.9%;  $P<0.01$ ), and coronary artery disease (88.6% versus 77.5%;  $P<0.01$ ) were all more frequent in cases. Use of angiotensin-converting enzyme inhibitors (ACEI) and beta blockers was similar between cases and controls while use of angiotensin receptor blockers (ARBs) was higher among controls (6.8% versus 12.2%,  $P=0.05$ ).

### Prevalence of QRS Fragmentation and Other ECG Parameters

The ECGs were performed a median of 313 days prior to the SCD event (range 2 to 5094), with 75% being performed within 3 years of the SCD event. The prevalence of the specified ECG parameters among cases and controls is outlined in Table 2. QRS fragmentation in any territory was detected in 64 (34.6%) cases and 109 (26.9%) controls, with

higher prevalence in cases ( $P=0.06$ ). When stratified by coronary artery territory, fragmentation was most frequently seen in the inferior territory in cases as well as controls. While there was no significant difference between cases and controls with regard to inferior (28.1% versus 23.7%;  $P=0.25$ ), and anterior territory fragmentation (9.7% versus 5.9%;  $P=0.10$ ), lateral fQRS was significantly more likely to be seen in cases compared with controls (8.1% versus 2.5%;  $P<0.01$ ; Figure 2). Cases were also significantly more likely than controls to have fragmentation in 2 or more anatomic territories (9.7% versus 4.9%;  $P=0.02$ ; Figure 3). There were 3 (1.6%) cases with fragmentation in all 3 anatomic territories, compared with none in the control group. The frequency of pathologic Q waves was not significantly different between cases and controls (14.8% versus 10.0%;  $P=0.09$ ).

With regard to other ECG parameters, mean heart rate was significantly higher in cases compared with controls ( $77.8\pm 16.9$  versus  $68.1\pm 14.0$  bpm;  $P<0.01$ ). Cases were also more likely to have borderline (15.3% versus 9.9%) or abnormal QTc (23.5% versus 7.2%; both  $P<0.01$ ) compared with controls ( $P<0.01$ ). There was no significant difference in QRS duration ( $87.9\pm 10.1$  versus  $87.3\pm 8.3$ ;  $P=0.50$ ).

**Table 1.** Demographic and Clinical Characteristics of Subjects

	Case (n=185)	Control (n=405)	P Value
Age, y	64.9 $\pm$ 13.8	64.9 $\pm$ 11.0	0.98
Male	124 (67.0)	262 (64.7)	0.58
Body mass index			0.53
Overweight	83 (44.9)	193 (47.7)	
Obese	102 (55.1)	212 (52.3)	
Left ventricular function			<0.001
Normal function	71 (65.1)	192 (73)	
Mild to moderate dysfunction	22 (20.2)	59 (22.4)	
Severe dysfunction	15 (14.6)	12 (4.7)	
Diabetes mellitus	81 (43.8)	121 (29.9)	<0.001
Cholesterol, mg/dL	182 $\pm$ 44	177 $\pm$ 48	0.34
Current/former smoker	116 (75.8)	201 (67.4)	0.07
Hypertension	143 (77.3)	286 (70.6)	0.09
Coronary artery disease*	164 (88.6)	314 (77.5)	<0.001
Use of angiotensin receptor blocker (ARB)	12 (6.8)	46 (12.2)	0.05
Use of angiotensin converting enzyme inhibitor (ACEI)	76 (43.2)	164 (43.6)	0.92
Use of beta blocker	95 (53.7)	226 (59.8)	0.17

Results presented as mean $\pm$ SD for continuous variables and n (%) for categorical variables. Body mass index categories: overweight (BMI 25 to 29.9 kg/m<sup>2</sup>), obese (BMI $\geq$ 30 kg/m<sup>2</sup>). Left ventricular function categories: ejection fraction (EF)  $\geq$ 55% (normal), EF 36–54% (mild-moderate dysfunction), EF  $\leq$ 35% (severe dysfunction); available for 109 cases and 263 controls. Cholesterol value available for 127 cases and 324 controls. Smoking status available for 153 cases and 298 controls. Data on use of angiotensin receptor blocker (ARB) and beta blocker were available for 177 cases and 226 controls. Data on use of angiotensin converting enzyme inhibitor (ACEI) were available for 176 cases and 376 controls. SCD indicates sudden cardiac death.

\*SCD cases  $\geq$ 50 years age assumed to have CAD based on >95% likelihood of CAD in such cases.<sup>26</sup>

**Table 2.** Electrocardiographic Characteristics of Cases and Controls

	Case (n=185)	Control (n=405)	P Value
fQRS distribution			
Any fragmentation	64 (34.6)	109 (26.9)	0.06
Inferior territory	52 (28.1)	96 (23.7)	0.25
Anterior territory	18 (9.7)	24 (5.9)	0.10
Lateral territory	15 (8.1)	10 (2.5)	<0.01
Q wave	27 (14.8)	40 (10.0)	0.09
QRS duration, milliseconds	87.9±10.1	87.3±8.3	0.50
Heart rate, beats per minute	77.8±16.9	68.1±14.0	<0.01
Corrected QT interval, milliseconds			<0.01
Normal	112 (61.2)	336 (83)	
Borderline	28 (15.3)	40 (9.9)	
Abnormal	43 (23.5)	29 (7.2)	

Results presented as n (%).QT interval categories: men ≤430 ms (normal), 431 to 450 ms (borderline), and >450 ms (abnormal); women ≤450 ms (normal), 451 to 470 ms (borderline), and >470 ms (abnormal). fQRS indicates fragmented QRS.

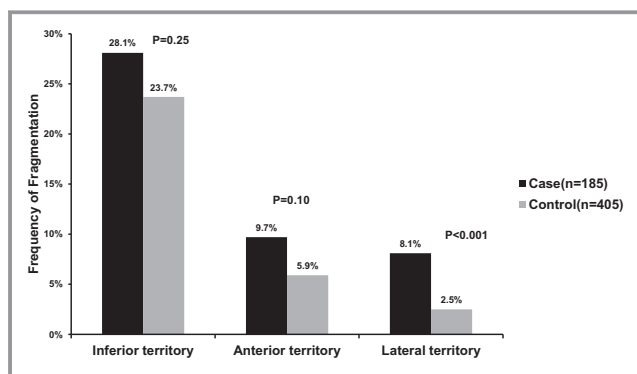
### Adjusted Odds Ratios for SCD

In a multivariable logistic regression model, presence of lateral territory fragmentation was significantly associated with SCD (OR=2.84; 95% CI 1.01 to 8.02; P=0.05) after adjustment for covariates significant in the univariate analysis. Other significant parameters included severe LV dysfunction (OR=3.55; 95% CI 1.54 to 8.21; P<0.01), abnormal QTc (P<0.01), and abnormal heart rate (P=0.02; Table 3).

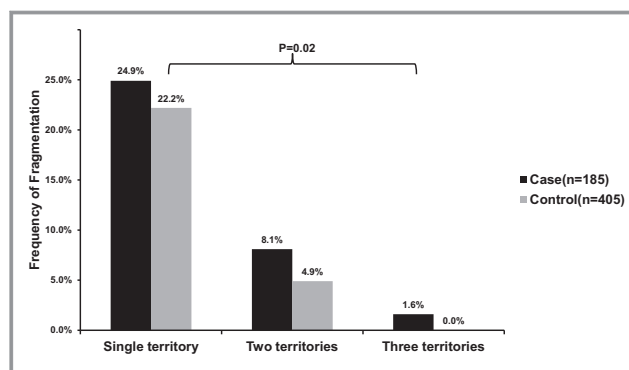
### Discussion

To the best of our knowledge this is the first evaluation of the potential association between QRS fragmentation on ECG and SCD, in a community-based obese/overweight population. The findings of this study could be important both from a

mechanistic as well as risk stratification perspective. Firstly, there was a higher prevalence of fragmentation overall among SCD cases compared with controls. Secondly, fragmentation in the lateral coronary territory was significantly associated with increased SCD odds even after adjustment for reduced EF and other ECG parameters. Thirdly, SCD cases were also distinguished by a greater burden of fragmentation in that they were more likely to have fragmentation in 2 or more anatomic territories. Increased heart rate and QT interval were also significantly associated with increased SCD odds which is consistent with earlier reports.<sup>30,31</sup> Importantly, presence of pathologic Q waves was not significantly different between cases and controls in this population. This is in concordance with prior studies which have shown that fragmented QRS complexes are more sensitive at detecting myocardial scar<sup>32</sup> and predict cardiac events even after resolution of Q waves.<sup>33</sup> Furthermore, since fragmentation, unlike Q waves owes its



**Figure 2.** Prevalence of fragmented QRS complexes (fQRS) by coronary artery territory in cases and controls.



**Figure 3.** Number of anatomic territories with QRS fragmentation in cases and controls.

**Table 3.** Multivariable Adjusted Odds Ratios for SCD

	Odds Ratio (95% CI)	P Value
Lateral fragmentation	2.84 (1.01 to 8.02)	0.05
Severe left ventricular dysfunction	3.55 (1.54 to 8.21)	<0.01
Abnormal QT interval	3.70 (1.97 to 6.96)	<0.01
Abnormal heart rate	3.55 (1.24 to 10.14)	0.02
Age	1.01 (0.99 to 1.03)	0.25
Diabetes mellitus	1.73 (1.05 to 2.85)	0.03
Coronary artery disease	0.73 (0.32 to 1.69)	0.47
Use of angiotensin receptor blocker	0.51 (0.21 to 1.28)	0.15

95% CI=95% confidence interval. Severe Left ventricular dysfunction defined: EF  $\leq$ 35%; abnormal QT interval categories: Men  $>$ 450 ms and Women  $>$ 470 ms; abnormal heart rate: heart rate  $>$ 100 bpm. EF indicates ejection fraction; SCD, sudden cardiac death.

genesis to inhomogeneous myocardial conduction, it may reflect other causes of delayed conduction as well, such as myocardial fatty infiltration, which may be especially relevant in the obese/overweight.<sup>34</sup> In arrhythmogenic right ventricular dysplasia (ARVD), characterized by fibrous/fatty replacement of right ventricular myocardium, fQRS has diagnostic value<sup>35</sup> and also predicts arrhythmic events.<sup>36</sup> Additionally, the utility of fQRS in conditions such as cardiac amyloidosis<sup>37</sup> supports the concept that fQRS may be a broader marker of myocardial infiltration beyond CAD-related scar.

Of note, fQRS remained significantly associated with SCD even after accounting for low LVEF. Reduced LVEF, while important, does not encompass the entire spectrum of adverse cardiac remodeling. For instance, fibrosis detected by cardiac magnetic resonance (CMR) has been reported to predict SCD beyond LVEF.<sup>38</sup> In this context, fQRS has been shown to correlate with subclinical LV dysfunction and adverse cardiac events in patients with preserved LVEF.<sup>39</sup> It has also been shown to correlate with ventricular dyssynchrony<sup>40</sup> and regression of fQRS with response to cardiac resynchronization therapy.<sup>41</sup> Thus, being a more sensitive marker of an adverse myocardial substrate, fQRS may have special relevance for SCD risk stratification in the obese/overweight. While the exact pathophysiologic pathways linking obesity to SCD remain to be elucidated, it is likely that the deleterious alterations in cardiac structure known to occur in obesity, including ventricular dilatation,<sup>10</sup> cardiac hypertrophy,<sup>11,12</sup> fibrofatty change,<sup>42</sup> and myocardial lipid accumulation<sup>43</sup> play an important role. Such changes may lead to increased cardiac irritability reflected by a greater burden of ventricular ectopy<sup>44</sup> and a greater tendency to develop atrial fibrillation.<sup>45</sup>

In this study, lateral fragmentation was associated with SCD. Conversely, an analysis from the MADIT II population reported that inferior fQRS was more predictive of SCD.<sup>19</sup> However, the

latter study was conducted on a heart failure/defibrillator population, distinct from our evaluation in the general population. Another study assessing fragmentation in the general population also reported an association between lateral fQRS and arrhythmic mortality, similar to the present study.<sup>46</sup> It is possible that different patterns of fragmentation may have relevance in different risk groups. Additionally, the quantitative burden of fragmentation, reflected by the number of leads with fragmentation, is likely to be important as well.<sup>47,48</sup>

Though fQRS appears promising as a risk marker, whether it can be used clinically to aid decision making for primary prevention of SCD needs further investigation. While there is accumulating evidence that fQRS predicts both arrhythmic events and appropriate ICD shocks,<sup>18,19</sup> a large multisite study among patients with LVEF  $\leq$ 35% found no evidence that fQRS would be useful in risk stratifying patients eligible for primary prevention ICD.<sup>49</sup>

Strengths of the present study include its population-based nature, prospective ascertainment and adjudication of SCD cases, as well as availability of detailed lifetime clinical history for both cases and controls. However, any study of this nature is subject to certain limitations. The study was performed on obese/overweight subjects only and may not apply to the overall population. We had to restrict the analysis to those with appropriate ECGs available which could lead to some bias in selecting patients with higher cardiac risk. On the other hand, given the burgeoning obese population and the close association of obesity with cardiovascular risk, this group represents a potentially important target for aggressive prevention. The wide confidence intervals of the effect estimates likely reflect the limited number of subjects; however, these were identified from a population of approximately 1 million, highlighting the practical difficulties of studying such subjects in the general population. While adjustment for a more comprehensive list of variables could not be carried out, at present EF is the only parameter used for SCD risk stratification and fragmentation may help improve risk prediction beyond EF. Further studies will be needed to clarify the exact mechanisms linking fragmentation in specific territories to arrhythmogenesis. We could not precisely estimate the prevalence of fragmentation among subjects without CAD as a good proportion of cases without previously diagnosed CAD may in fact have underlying CAD, as has been demonstrated by prior autopsy studies of SCD in the general population.<sup>25</sup> Finally, further prospective studies assessing the role of fQRS in a variety of high-risk groups in the population will be needed prior to its application in the clinical arena.

## Conclusion

In this population-based study among obese/overweight subjects, QRS fragmentation in the lateral territory was

associated with increased SCD risk even after adjustment for LVEF. Obese SCD subjects were also characterized by a greater likelihood of fragmentation in 2 or more coronary territories. The utility of fragmentation for SCD risk stratification in subjects with high BMI warrants further evaluation.

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## Disclosures

None.

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