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 (≥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.”1,2 Obesity is closely associated with the metabolic syndrome3 and has been linked to adverse cardiovascular prognosis and mortality.4,5 A diagnosis 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.6

Large cohort studies7,8 as well as population-based analysis from the Oregon Sudden Unexpected Death Study (SUDS)9 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,10 as well as left ventricular hypertrophy and diastolic dysfunction.11,12 Recent animal13 as well as clinical14 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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Received November 28, 2014; accepted February 5, 2015.

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DOI: 10.1161/JAHA.114.001654

Journal of the American Heart Association

been published earlier.22

out-of-hospital SCD. Detailed methods and descriptions have been published earlier.

The Oregon SUDS is a prospective, population-based study of subjects in the community. We therefore undertook a systematic investigation of the potential utility of QRS fragmentation, 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.22-24 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.25 CAD was defined as ≥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 ≥50 years of age were assumed to have CAD based on ≥95% likelihood of CAD in such cases.26 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 (≥55%), mild to moderate dysfunction (36-54%), or severe dysfunction (≤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/m², and obesity was defined as a BMI of ≥30 kg/m².27 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,15 the present analysis was limited to ECGs with narrow QRS (QRS duration <120 ms). The QT interval was corrected using Bazett’s formula28 and categorized as normal or abnormal using sex-specific criteria (men: QTc ≤430 ms—normal, 431 to 450 ms—borderline, >450 ms—abnormal; women: QTc ≤450 ms—normal, 451 to 470 ms—borderline, >470 ms—abnormal).29 Pathologic Q waves were defined as Q waves ≥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 defined15 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 ≥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 χ² tests were used for comparisons of continuous variables (presented as mean±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 (≥100 versus <100 bpm) were categorized based on accepted standards. Results were reported as 2-tailed P values, with a P value of ≤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 ≤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 (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±16.9 versus 68.1±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±10.1 versus 87.3±8.3; \(P=0.50\)).

Table 1. Demographic and Clinical Characteristics of Subjects

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

Results presented as mean±SD for continuous variables and n (%) for categorical variables. Body mass index categories: overweight (BMI 25 to 29.9 kg/m²), obese (BMI≥30 kg/m²). Left ventricular function categories: ejection fraction (EF) ≥55% (normal), EF 36–54% (mild-moderate dysfunction), EF ≤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 ≥50 years age assumed to have CAD based on >95% likelihood of CAD in such cases.26
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. 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 and predict cardiac events even after resolution of Q waves. Furthermore, since fragmentation, unlike Q waves owes its
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Table 3. Multivariable Adjusted Odds Ratios for SCD

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

95% CI=95% confidence interval. Severe Left ventricular dysfunction defined: EF ≤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.

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.19 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.46 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.47,48

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.

Acknowledgments
The authors would like to acknowledge the significant contribution of American Medical Response, Portland/Gresham fire departments, and the Oregon State Medical Examiner’s office.

Sources of Funding
Funded in part, by National Heart, Lung, and Blood Institute grants R01HL088416 and HL105170 to Dr Chugh. Dr Chugh holds the Pauline and Harold Price Chair in Cardiac Electrophysiology Research at the Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA.

Disclosures
None.

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*J Am Heart Assoc.* 2015;4:e001654; originally published March 11, 2015;
doi: 10.1161/JAHA.114.001654

The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980

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