Body Mass Index as a Predictor of Sudden Cardiac Death and Usefulness of the Electrocardiogram for Risk Stratification

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Evidence of the role of body mass index (BMI) as a risk factor for sudden cardiac death (SCD) is conflicting, and how electrocardiographic (ECG) SCD risk markers perform in subjects with different BMIs is not known. In this study, a general population cohort consisting of 10,543 middle-aged subjects (mean age 44 years, 52.7% men) was divided into groups of lean (BMI <20, n = 374), normal weight (BMI 20.0 to 24.9, n = 4,334), overweight (BMI 25.0 to 29.9, n = 4,390), and obese (BMI >30, n = 1,445) subjects. Cox proportional hazards models adjusted for confounders were used to assess the risk for SCD associated with BMI and the risk for SCD associated with ECG abnormalities in subjects with different BMIs. The overweight and obese subjects were at increased risk for SCD (hazard ratios [95% CIs] were 1.33 [1.13 to 1.56], p = 0.001 and 1.79 [1.44 to 2.23], p <0.001 for overweight and obese subjects, respectively). The risk of non-SCD had a similar relation with BMI as SCD. Hazard ratios associated with ECG abnormalities were 3.03, 1.75, 1.74, and 1.34 in groups of lean, normal weight, overweight, and obese subjects, respectively, but no statistical significance was reached in the obese. ECG abnormalities improved integrated discrimination indexes and continuous net reclassification indexes statistically significantly only in the normal weight group. In conclusion, the overweight and obese are at increased risk for SCD but also for non-SCD, and ECG abnormalities are associated with increased risk of SCD also in normal weight subjects presenting with less traditional cardiovascular risk factors. **(Am J Cardiol 2016;117:388−393)**

Obesity is a major global health problem and an independent risk factor for cardiovascular disease.[1,2] Obesity has been shown to be associated with multiple structural and functional abnormalities in the heart, some of which might predispose obese subjects to arrhythmias.[2] Sudden cardiac death (SCD) is a major cause of cardiovascular mortality in this population, but in many cases, SCD may be the first manifestation of heart disease.[3] However, epidemiologic data on the impact of body mass index (BMI) to the risk of SCD are somewhat conflicting, although strong associations have been shown between measures of abdominal obesity and the risk for SCD.[4,5] During the past years, a plethora of research has focused on different risk stratification strategies, including electrocardiography, to predict the risk of SCD and has been able to identify several electrocardiographic (ECG) risk markers of SCD.[3] Obesity also influences multiple ECG measures,[6] but how the established ECG risk markers perform in the obese is not known. In this study, we wanted to examine the relation between the BMI and the risk for SCD and to test how ECG abnormalities associated with SCD perform in lean, normal weight, overweight, and obese subjects.

Methods

The study population consists of 10,957 men and women aged 30 to 59 years who took part in the Social Insurance Institution's Coronary Heart Disease study from 1966 to 1972, which was carried out in 35 populations of different geographical areas in Finland well representing the Finnish middle-aged population. The overall participation rate was 89.6% (total 12,310 invited subjects). We excluded subjects with unreadable or missing ECGs, subjects presenting with atrial fibrillation, atrial flutter, Wolff−Parkinson−White pattern, 2nd or 3rd degree atrioventricular block, or pacemaker rhythm, and subjects with missing data. Most exclusions were made because of missing or unreadable ECGs (n = 53), missing blood pressure (n = 128), and unreliable assessment of QT interval (n = 50), fragmented QRS

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(fQRS; n = 87), Romhilt−Estes point score (n = 100), or QRS/T angle (n = 124). Subjects in whom the assessment of QRS/T angle, fQRS, or T-wave inversions was not performed because of bundle branch blocks or wide QRS were included in the analysis. We were left with 10,543 subjects. The study rationale and procedures performed at the baseline examinations have been described previously.[7] Briefly, in the baseline examination, a standard 12-lead ECG was recorded with the subject at rest in supine position at paper speed of 50 mm/s and calibration of 1 mV/10 mm, and blood pressure, BMI, and serum cholesterol were measured. The subjects also completed a questionnaire regarding their health habits, known diseases, drug therapy, and smoking habits. All symptoms of cardiovascular disease were documented during the examination. We classified subjects with BMI <20 as lean, BMI 20 to 24.9 as normal weight, BMI 25.0 to 29.9 as overweight, and BMI >30 obese as recent data suggest that the relation between BMI and cardiovascular mortality might be J-shaped.[8] When the original study was conducted, there were no institutional review committees and universal practice was that subjects gave their consent by participating in the study.

The subjects were followed from the baseline examination for 35 to 41 years until the end of 2007. The amount of subjects lost to follow-up was <2%, but for the majority of this group, the survival status could still be determined. The mortality data were obtained from the Causes of Death Register maintained by Statistics Finland. The accuracy of this register has been validated previously.[9] The death certificates were obtained for each deceased subject. All deaths from cardiac causes were reviewed by 2 experienced cardiologists (OA. and HVH.) by the use of hospital records and necropsy reports, if available, to identify sudden deaths from arrhythmia on the basis of the definitions presented in the Cardiac Arrest Pilot study,[10] as described by our group previously.[11]

The ECGs recorded during the baseline examinations were interpreted by 9 trained readers and coded according to the revised Minnesota code (MC).[7,12] In addition, QTc interval (according to Bazett's formula) and Romhilt−Estes point score were assessed. The ECGs were later independently reevaluated by 5 physicians who were unaware of the original measurements for the presence of early repolarization patterns,[11] intraventricular conduction delay (IVCD),[13] bundle branch blocks,[13] abnormal QRS/T angle,[14] T-wave inversions,[15] and fQRS complex.[16] The ECG abnormalities studied in this study were chosen on the basis of previous evidence of their association with SCD.[3] We chose to divide the ECG abnormalities into major abnormalities and other abnormalities as in previous studies[17] to enable comparison. The criteria for major abnormality were any of the following: Q and QS patterns (MC 1-1 and 1-2), left ventricular hypertrophy (defined by Romhilt−Estes point score ≥5), left bundle branch block or IVCD, horizontal or downsloping ST-segment depressions at least 0.5 mm deep (MC 4-1 and 4-2), and ≥1.0 mm deep T-wave inversions in leads other than aVR, aVL, III, and V1 to V3. Right bundle branch block and T-wave inversions in leads V1 to V3 were not classified as abnormalities as they were not associated with mortality in this population.[13,15] The criteria for other abnormality were any of the following: an early repolarization pattern with inferior J point elevation ≥0.1 mV with horizontal or downsloping ST-segment, QTc ≥450 ms in men and ≥460 ms in women,[18] QRS/T angle ≥100°, and lateral fQRS pattern. Subjects presenting with both major and other abnormalities were coded as having major abnormalities.

The differences in baseline characteristics of subjects in the BMI groups were assessed by analysis of variance for continuous variables and the chi-square test for categorical variables. The primary outcome was SCD. The hazard ratios (HRs) and their 95% CIs for SCD were calculated using the Cox proportional hazards model. The covariates were selected on the basis of previous evidence of an association with cardiovascular mortality. Gender, smoking status, baseline cardiac disease, and diabetes status were used as categorical variables, and age, systolic blood pressure, and blood cholesterol were used as continuous variables. The follow-up time was defined as the number of days from the baseline examination to the day of death or end of follow-up, whichever came first. The value of ECG predictors of SCD in risk stratification was assessed by calculating the change in C statistic, continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI).[19] The other ECG abnormalities variable was added to a model with major abnormalities variable already included. These analyses were conducted separately for lean, normal weight, overweight, and obese subjects. All p values are 2-sided. The statistics analyses were made with R, version 3.1.2, (*http://www.R-project.com* packages survC1 and survIDINRI) and with the Statistical Package for Social Studies, version 22.

Results

Of 10,543 subjects in the analyses, 3.5% were classified as lean, 41.1% as normal weight, 41.6% as overweight, and 13.7% as obese. The baseline characteristics of subjects by BMI groups are presented in Table 1. Subjects with higher BMIs were generally older, had higher blood pressures, and also, cardiovascular disease was more common in them.

During the follow-up, 56.2% of the study population died. 33.1% of all deaths were cardiac and 13.0% of all deaths were classified as SCD the mortality being higher in subjects with higher BMIs and in men. The proportion of sudden deaths of cardiac deaths did not differ significantly between the BMI groups. The numbers of death and the proportion of sudden deaths of cardiac deaths by BMI group are presented in Table 2. These numbers for men and women separately are presented in Supplementary Table 1. On the basis of a Cox proportional hazards model, the overweight and obese were at increased risk for SCD. The results of this model are presented in Table 3. These results for men and women separately are presented in Supplementary Table 2. The analyses were also conducted separately for subjects free of ECG abnormalities and baseline cardiac disease (n = 8,207) with largely similar results the multivariate-adjusted HRs being 0.99 (95% CI 0.74 to 1.83, p = 0.976), 1.41 (95% CI 1.15 to 1.73, p = 0.001), and 1.85 (95% CI 1.41 to 2.44, p <0.001) for lean, overweight, and obese subjects, respectively. We also conducted similar models in the whole population with non-SCD as the end point to see if there were differences in