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ST-elevation myocardial infarction risk in the very elderly

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ABSTRACT

Background: Despite the high incidence and mortality of ST-segment elevation myocardial infarction (STEMI) among the very elderly, risk markers for this condition remain poorly defined. This study was designed to identify independent markers of STEMI among individuals carefully selected for being healthy or manifesting STEMI in <24 h.

Methods: We enrolled participants aged 80 years or older of whom 50 were STEMI patients and 207 had never manifested cardiovascular diseases. Blood tests, medical and psychological evaluations were obtained at study admission. Odds Ratio (OR) and attributed risk (AR) were obtained by multivariate regression models using STEMI as dependent variable.

Results: Low glomerular filtration rate (GFR) [OR:4.41 (1.78–10.95); $p = 0.001$], reduced levels of HDL-C [OR:10.70 (3.88–29.46); $p = 0.001$], male gender [OR:12.08 (5.82–25.08); $p = 0.001$], moderate to severe depressive symptoms [OR:10.00 (2.82–35.50); $p = 0.001$], prior smoking [OR:2.00 (1.05–3.80); $p = 0.034$] and current smoking [OR:6.58 (1.99–21.70); $p = 0.002$] were significantly associated with STEMI. No association was found between STEMI and age, diabetes, hypertension, mild depressive symptoms, triglyceride or LDL-C.

Conclusions: This is the first case–control study carried out with very elderlies to assess STEMI risk. Our findings indicate that reduced HDL-C, GFR, male gender, smoking habits and moderate to severe depressive symptoms are markers of STEMI in this age group.

General Significance: In Individuals aged 80 or more years, a greater attention must be paid to low HDL-C and GFR at the expense of conventional STEMI risk factors for younger adults such as diabetes mellitus, hypertension and high LDL-C or triglyceride.

1. Introduction

The 20th century was marked by a 300% increase in the elder population in developed countries [1]. Impressively, another similar increase is expected to take place in half of that time in the present century [2]. In developing countries such as China, Brazil, and Colombia, the growth of the aged population is occurring 3-times faster as compared with developed countries [3]. As one might expect, such rapid growth in longevity has generated a new demographic profile in which there is a larger proportion of individuals 80 years or more.

It is well known that both the incidence and mortality from cardiovascular disease (CVD) in the elderly rises with age [4]. Indeed, the mortality rate after ST-segment elevation myocardial infarction (STEMI) in these individuals is 10-fold higher than in those with 65 years or less [5]. These figures are probably underestimated, considering the difficulty of access to emergency units due to walking difficulties or cognitive dysfunction commonly found among these individuals.

Although primary prevention would certainly be the best strategy for reducing morbidity and mortality related to STEMI, there is currently insufficient data to identify risk predictors in this specific population of patients. In addition, the combined effect of the enhanced incidence and

Abbreviations: CVD, cardiovascular disease; STEMI, ST-segment elevation myocardial infarction; BHS, Brasília Heart Study; MI, myocardial infarction; CK-MB, MB fraction of creatine kinase; BSHA, Brasília Study on Healthy Aging; BDI-II, Beck Depression Inventory version II; GDS, Geriatric Depression Scale; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; EDTA, ethylenediamine tetraacetic acid; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GFR, glomerular filtration rate; SD, standard deviation; IQR, interquartile range; ANCOVA, analysis of covariance; OR, odds ratio; AR, attributable risk.

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mortality from STEMI may favor a selection bias that can distort the association with traditional risk factors and potentially hinder the identification of new ones. In this context, we compared two cohorts of very elderly individuals (≥80 years) who are healthy or in the first hours after STEMI in order to identify independent risk markers.

2. Material and methods

2.1. Study design and participants

For the present study, cases and controls were selected in a one-to-four ratio matching for age based on two studies databases. Only patients 80 years or older from the Brasília Heart Study (BHS) database were selected for analysis ($n = 50$). BHS is a prospective ongoing observational cohort enrolling STEMI patients admitted at the Hospital de Base do Distrito Federal (Brasília, Brazil) since 2006. BHS inclusion criteria was: (i) <24 h after onset of MI symptoms, (ii) ST-segment elevation of at least 1 mm (frontal plane) or 2 mm (horizontal plane) in 2 contiguous leads and (iii) increased myocardial necrosis markers above reference limit of CK-MB (25 U/L) and troponin (0.04 ng/mL) followed by a decline of both markers. Exclusion criteria were (i) cognitive impairment, (ii) inability to attend follow-up and (iii) other comorbidities that lead to significantly shorter life expectancy. BHS is registered at ClinicalTrials.org (NCT02062554) [6].

The control group was composed of individuals consecutively enrolled in the Brasília Study on Healthy Aging (BSHA) ($n = 207$). BSHA is a prospective cohort of healthy very elderly individuals (80 to 102 years) who voluntarily accepted to participate and were followed at the outpatient clinic of the Biocardios Institute of Cardiology (Brasília, Brazil) since 2008. Exclusion criteria were (i) manifested atherosclerotic disease (MI, stroke, or peripheral arterial disease) as indicated by a medical evaluation, electrocardiogram or echocardiogram, (ii) functional dependence or institutionalization, (iii) cognitive impairment assessed by mini-mental state examination (<13 points), (iv) use of any anti-inflammatory drugs in the last 30 days, (v) current or previous diagnosis of neoplastic or immune inflammatory disease, (vi) chronic obstructive pulmonary disease, (vii) glomerular filtration rate < 25 mL/min/1.73 m^2, (viii) hepatic disease (aspartate or alanine transaminases ≥1.5 upper reference limit), (ix) chronic infectious disease (≥3 months), (x) left ventricle ejection fraction <50% on echocardiography and (xi) neoplastic disease at admission or until the first year after enrollment. Neoplastic disease was investigated through evaluation of fecal occult blood, mammography and clinical breast exam, prostate-specific antigen plasma assay, digital rectal examination and Papanicolaou smear analysis according to current guidelines [7]. BSHA is registered at ClinicalTrials.gov (NCT02366104) [8].

Both studies were carried out in accordance with The Declaration of Helsinki [9], and were approved by the local Ethics Committee (BHS: 083/06 and BSHA: 213/08). Informed consent was obtained from all individual participants included in the study.

2.2. Clinical and psychological evaluation

All participants underwent a structured detailed clinical questionnaire, anthropometric measurements, blood collection and psychological tests. Depressive symptoms manifested in the last weeks before STEMI (BHS study) or before the admission into the BSHA study were evaluated by the use of Beck Depression Inventory version II (BDI-II) or Geriatric Depression Scale (GDS), respectively. These two self-reported inventories were validated in this age group and have shown to be highly correlated [10]. Ex smoking status was defined as smoking cessation for at least 6 months. Diabetes was defined as the use of anti-diabetic medications, fasting glycaemia ≥126 mg/dL or glycated hemoglobin (HbA1c) ≥6.5%. Hypertension was defined by the use of antihypertensive drugs or by the systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg.

2.3. Biochemical analysis

Among STEMI patients, blood samples were obtained in the first 24 h from MI symptoms in order to avoid the reported lipid profile changes that occur after this time window [11]. Among controls, blood samples were obtained at admission. Blood samples with EDTA were centrifuged after collection at 5 °C and at 4500 rpm for 15 min to separate plasma and cells. Biochemical analyses were performed in duplicates. An automatic chemical analyzer was used to do the following analysis: C-reactive protein (CRP; high-sensitivity assay, Cardiophase, Dade Behring, Marburg, Germany), total cholesterol (CHOD-PAP, Roche Diagnostics, Mannheim, USA), high-density lipoprotein cholesterol (HDL-C, Roche Diagnostics, Mannheim, USA), triglycerides (GPO-PAP, Roche Diagnostics, Mannheim, USA), urea and creatinine (GLDH, Hitachi, Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. Glomerular filtration rate (GFR) was estimated by abbreviated MDRD equation: Estimated GFR (mL/min/1.73 m^2) = 186 × (creati-(creatinine/88.4)$^{-1.154}$ × (age) $^{-0.203}$ × (0.742, if female) × (1.210, if black) [12].

2.4. Statistical analysis

Normal data are presented as mean ± SD and skewed data as median and interquartile range (IQR). Categorical and continuous baseline data were tested using chi-square and t-Student tests, respectively. Analyses of covariance (ANCOVA) with adjustments for gender and age were performed for comparison of mean change from the baseline. Assumptions of the ANCOVA models (linearity, normality of distribution and equal variance) were checked using histograms, normal probability plots and residual scatter plots. Ordinal logistic regression analyses were used to assess the association between the presence of STEMI and the following continuous variables categorized into tertiles: age, LDL-C, HDL-C, triglyceride levels and GFR. Binary logistic regression was used to assess the association between STEMI and categorical binary data: gender, diabetes mellitus, hypertension, depressive symptoms, and current/ex smoking. Odds ratios (OR) for STEMI are reported across individual risk factors in unadjusted and fully adjusted models. For all multivariable procedures, variables that displayed a p-value <0.05 in univariate analyses were selected as covariable. Attributable Risk (AR) was used to estimate the impact of each risk marker of STEMI in the very elderly. Statistical analysis was performed using SPSS®, version 21 for Mac (IBM) and SAS Analytics®, version U for Mac (SAS Institute Inc.) for AR. Probability value of <0.05 was considered statistically significant.

3. Results

3.1. Clinical and laboratorial characteristics

Clinical and laboratorial baseline characteristics of study participants are in Table 1. Higher frequency of female gender and higher levels of HDL-C and GFR were found in controls. Moderate to severe depressive symptoms, prior and current smoking were more frequently found in cases. Controls had quit smoking for longer than cases (32 ± 17 *vs.* 20 ± 12 years; $p = 0.027$).

3.2. STEMI risk markers

Table 2 shows all individual categorical risk markers in unadjusted analysis (Model 1) and after fully adjustment (Model 2). In order to avoid over-fitting, prior and current smoking status were pooled together as smoking. Based on the univariate analysis, selected covariates for adjustments were: gender, depressive symptoms, smoking, GFR, and HDL-C.

Although the age of participant ranged between >2 decades, it was not related to STEMI occurrence. In contrast, reduced levels of GFR or HDL-C were associated with STEMI in both unadjusted and fully