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Is there a heart rate paradox in acute heart failure?

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ABSTRACT

Background: Higher heart rate predicts higher mortality in chronic heart failure (HF). We studied the prognostic impact of admission heart rate in acute HF and analysed the importance of its change during hospitalization.

Methods: Acute HF patients were studied. Endpoint was all-cause death. Patients were followed-up for 12 months from hospital admission. Cox-regression analysis was used to study the association of heart rate (both as a continuous and as a categorical variable) with mortality. Analysis was stratified according to admission rhythm and to systolic dysfunction. Multivariate models were built. Patients surviving hospitalization were additionally cross-classified attending to admission and discharge heart rates – cut-offs: 100 and 80 beats per minute (bpm), respectively.

Results: We analysed 564 patients. Median age was 78 years and median admission heart rate 87 bpm. In a 12-month period 205 patients died, 23 in-hospital. Mortality increased steadily with heart rate decrease. Patients with heart rate ≥100 bpm had a multivariate-adjusted HR of 12-month death of 0.57 (95%CI: 0.39–0.81), and the HR was 0.92 (0.85–0.98) per 10 bpm increase in heart rate. Association of heart rate with mortality was stronger in patients in sinus rhythm (SR) and in those with systolic dysfunction. Eighty-seven patients had admission heart rate ≥100 and discharge heart rate <80 bpm. In them, death rate was 14.9%; in the remaining patients it was 37.7%.

Conclusions: Higher admission heart rate predicted survival advantage in acute HF. Patients presenting with tachycardia and discharged with a controlled heart rate had better outcome than those admitted non-tachycardic or discharged with a non-controlled heart rate.

1. Introduction

Tachycardia predicts coronary artery disease development [1] and cardiovascular morbidity and mortality both in the general population and in patients with ischemic heart disease [2–7]. Increased resting heart rate associates with increased risk of incident heart failure (HF) [8] and predicts mortality in chronic HF patients [9–12]. Resting heart rate is not only seen as a risk marker in HF but also as a risk factor since heart rate reduction results in cardiovascular risk reduction [13–18]. The impact of heart rate in the prognosis of chronic HF patients and its higher relative importance when compared with beta blockers use and dose has been suggested [19,20]. The prognostic impact of heart rate in acute HF is less well studied. A recent large retrospective study suggested that higher heart rate was independently associated with higher in-hospital mortality in acute HF patients [21]. Higher heart rate in acute HF patients presenting in the emergency department also predicted higher 7-day mortality [22]. These observations lead to the inclusion of admission heart rate in risk scores for the assessment of short-term prognosis in acute HF [23,24].

We studied the prognostic impact of admission heart rate in acute HF patients and analysed if prognostic implications differed between patients in sinus rhythm (SR) and those in atrial fibrillation (AF); and between patients with left ventricular systolic dysfunction and those with HF with preserved ejection fraction. We also evaluated the impact of heart rate change during hospitalization.

2. Methods

Between January 2009 and December 2010 a registry of acute HF was conducted in the Internal Medicine department of Hospital São João, Porto, Portugal, which is a tertiary care academic hospital. As part of the registry's protocol all patients admitted to our department with the primary diagnosis of acute HF were eligible for inclusion in the registry. Both acute *de novo* and worsening chronic HF patients

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were studied. The 2008 European Society of Cardiology guidelines were used for the diagnosis of HF [25]. An echocardiogram was performed to all patients during hospitalization and both patients with systolic dysfunction and those with HF with preserved ejection fraction were included in the registry. Left ventricular ejection fraction >50% was considered preserved systolic function. Exclusion criteria for registry inclusion were: 1) acute coronary syndromes as the cause of acute HF and 2) patients whose symptoms were explained by conditions other than HF. The registry's protocol conforms to the ethical guidelines of the declaration of Helsinki and it was approved by the local ethics committee. Patients provided informed consent. As part of the registry's protocol a complete physical examination at admission and in the discharge day was performed. A 12-lead electrocardiogram was performed at admission. Demographic characteristics, medications in use upon hospitalization, discharge medication and comorbidities were recorded. All patients were also drawn a venous blood sample within the first 48 h of hospital admission as well as in the discharge day. Plasma B-type natriuretic peptide (BNP) was measured by way of a chemiluminescent immunoassay using an Architect i2000® automated analyzer (Abbott, Lisbon, Portugal). Serum sodium, creatinine and C-reactive protein were measured using conventional methods with an Olympus AU5400® automated clinical chemistry analyzer (Beckman-Coulter®, Izasa, Porto, Portugal). Haemoglobin was obtained using an automated blood counter Sysmex® XE-5000 (Emilio de Azevedo Campos, Porto, Portugal). Physicians treating acute HF patients admitted during this time period were aware of the ongoing HF registry. The patients' treatment strategy, timing of discharge and discharge medication were at the discretion of the attending physician. Patients' hospitalizations and vital status were ascertained by consulting hospital registries and by telephone contact with the patients or their relatives.

We conducted a retrospective analysis on the patients prospectively included in this registry. The admission heart rate was defined as the first heart rate recorded in the emergency department, before any acute HF medication, whether recorded by a physician or the emergency department nurse staff. The discharge heart rate was the one recorded by an attending health care professional in the discharge day. We therefore additionally excluded the patients with no heart rate recording in the emergency department. We also excluded all the patients with permanent pacemaker, cardiac resynchronization therapy, and implantable cardioverter defibrillator. Patients' follow-up was considered from hospital admission. The endpoint under analysis was all-cause death at 12 months.

2.1. Statistical analysis

The prognostic impact of admission heart rate was first tested as a categorical variable: till 59 beats per minute (bpm), from 60 to 79 bpm, from 80 to 99 bpm and 100 bpm and above; and then analysed as a continuous variable (per 10 bpm). The cut-off of 100 bpm was chosen to dichotomize the variable. Comparisons between groups of patients were performed by: Chi square-test for categorical variables, Student's t test for normally distributed continuous variables and Mann–Whitney U test for skewed continuous variables. Variables independently associated with higher admission heart rate or with tachycardia were assessed using multivariate linear or logistic regression models, respectively. Prognostic prediction was made using Cox regression analysis. Variables in the 1-year mortality prediction model included those that were outcome-associated in a univariate approach (age, admission systolic blood pressure, admission sodium, haemoglobin and BNP) as well as potential confounders in the association of heart rate with mortality (previous use of beta blockers and digitalis, admission rhythm and left venticular systolic disfunction). The analysis of the prognostic impact of admission heart rate was additionally stratified according to the admission rhythm and also according to left ventricular systolic dysfunction.

Patients surviving the hospitalization due to acute HF were further cross-classified considering not only the admission heart rate (cut-off 100 bpm), but also the discharge heart rate (cut-off 80 bpm). For this analysis we excluded patients dying in-hospital (n = 23) as well as those with no record of discharge heart rate (n = 27). Multivariate models were built. Model 1 included variables associated with the outcome in a univariate approach; and model 2 also considered variables classically associated with mortality in HF patients as well as common comorbidities and potentially confounding factors.

Kaplan–Meier method was used to show and compare survival curves according to the 4 strata of admission heart rate and also according to the 4 groups created based on the admission and the discharge heart rate.

The p value considered for statistical significance was 0.05. Data was stored and analysed using SPSS software (IBM corp, Armonk, NY, version 20.0).

3. Results

A total of 564 patients were analysed. Median age was 78 years and median admission heart rate was 87 (range 35–170) bpm; 262 (46.5%) of the patients were admitted in AF and 303 (53.7%) had HF with reduced ejection fraction (Table 1). Thirty-two percent of the patients were tachycardic at admission. Table 1 also shows patients' characteristics according to admission heart rate (≥100 vs. <100 bpm). Tachycardic patients were significantly younger, had better renal function and higher haemoglobin; they more often had HF of non-ischemic aetiology; and they also had higher New York Heart Association (NYHA) functional class at admission. Tachycardic and non-tachycardic patients were similar concerning previous medication with beta blockers or digitalis but patients with higher heart rate were more often discharged under such medication. Importantly, no significant differences in BNP or prevalence of AF were noted between these patients. Neither beta blockers nor digitalis use were independently associated with higher heart rate or admission tachycardia.

During the 12-month follow-up period 205 patients died, 23 of them in-hospital (in-hospital mortality of 4.1%) and 182 after hospital discharge. Fig. 1 shows the Kaplan–Meier survival curves according to admission heart rate strata. There was a steady decrease in 12-month all-cause mortality with increasing admission heart rate. In a multivariate Cox-regression analysis patients with HR ≥100 bpm had a multivariate-adjusted HR of 12-month death of 0.57 (95%CI: 0.39–0.81), and the HR was 0.92 (0.85–0.98) per each 10 bpm increase in heart rate (see Table 2).

From the 262 patients admitted in AF, 101 died during follow-up. Patients admitted in AF were older, and more often had non-ischemic HF with preserved ejection fraction; they were also more often medicated with digitalis, but there were no differences concerning beta blocker use (before and after hospitalization). Importantly, no significant differences existed in admission heart rate (median of 88 bpm in SR vs 87 bpm in AF patients), as well as in heart rate decrease during hospitalization (mean decrease of 15 vs 16 bpm in SR and AF respectively). Table 2 shows the multivariate model considering the whole population and also when the analysis was stratified according to the admission rhythm. The protective effect of higher heart rate seems stronger in patients admitted in SR, although a protective point of estimate is maintained, particularly in the dichotomized analysis.

A total of 303 patients had HF of reduced ejection fraction and 110 of them died during follow-up. Table 3 represents the same multivariate model when the data are stratified according to left ventricular dysfunction. Again, there appears to be a stronger impact of admission heart rate in patients with HF with reduced ejection fraction.

We then cross-classified patients also attending to discharge heart rate (cut-off value of 80 bpm) in 4 groups: 1) patients admitted non-tachycardic and discharged with a non-controlled heart rate: n = 107; 2) patients admitted non-tachycardic and discharged with heart rate <80 bpm, n = 243; 3) patients admitted with ≥100 bpm and discharged with ≥80 bpm: n = 72; and 4) patients tachycardic at admission and