Resting heart rate at hospital admission and its relation to hospital outcome in patients with heart failure

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Abstract
Background: Resting heart rate (HR) has been proven to influence long-term prognosis in patients with chronic heart failure (HF). The aim of this study was to assess the relationship between resting HR at hospital admission and hospital outcome in patients with HF.

Methods: The study included Polish patients admitted to hospital due to HF who agreed to participate in Heart Failure Pilot Survey of the European Society of Cardiology.

Results: The final analysis included 598 patients. Median HR at hospital admission was 80 bpm. In univariate analyses, higher HR at admission was associated with more frequent use of inotropic support (p = 0.0462) and diuretics (p = 0.0426), worse clinical (New York Heart Association — NYHA) status at discharge (p = 0.0483), longer hospital stay (p = 0.0303) and higher in-hospital mortality (p = 0.003). Compared to patients who survived, patients who died during hospitalization (n = 21; 3.5%) were older, more often had a history of stroke or transient ischemic attack and were characterized by higher NYHA class, higher HR at admission, lower systolic and diastolic blood pressure at admission, lower ejection fraction, lower glomerular filtration rate, and lower natrium and hemoglobin concentrations at hospital admission. In multivariate analysis, higher HR at admission (OR 1.594 [per 10 bpm]; 95% CI 1.061–2.395; p = 0.0248) and lower natrium concentration at admission (OR 0.767 [per 1 mmol/L]; 95% CI 0.618–0.952; p = 0.0162) were the only independent predictors of in-hospital mortality.

Conclusions: In patients with HF, higher resting HR at hospital admission is associated with increased in-hospital mortality. (Cardiol J 2014; 21, 4: 425–433)

Key words: heart rate, heart failure, prognosis, in-hospital mortality, hyponatremia

Introduction
Over the last few decades, the incidence and prevalence of chronic heart failure (HF) have been constantly increasing. This is a result of growing life expectancy and aging of modern societies, as well as advances in the treatment of acute coronary syndromes which lead to an increased number of survivors with left ventricular dysfunction [1]. Randomized clinical trials and large-scale registries are both helpful research tools. However, contrary to clinical trials, the advantage
of registries is that they reflect real-life patient populations. The aim of the Heart Failure Pilot Survey of the European Society of Cardiology was to assess clinical profile, pharmacotherapy and clinical course in HF patients across Europe [2].

Despite recent progress in pharmaco- and electrotherapy, prognosis in HF remains poor. The Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial (SHIFT) demonstrated that in patients with chronic systolic HF higher resting heart rate (RHR) was associated with worse long-term prognosis [3]. The aim of this study was to assess the impact of RHR at hospital admission on short-term outcome in a Polish population of patients hospitalized for HF, based on data from the Heart Failure Pilot Survey.

Methods

Study population

The Heart Failure Pilot Survey was conducted by the European Society of Cardiology within the scope of the EURObservational Research Programme. It was a prospective, multicenter, observational survey of HF patients in 12 European countries. The survey included adult (i.e. over 18 years old) patients with HF — both, outpatients with HF seen in ambulatory care, as well as patients admitted to hospital for acute or chronic HF. There were no specific exclusion criteria. Patients were enrolled in the study if they presented to hospital or outpatient clinic on one particular day of the week (chosen by the participating center) from October 2009 to May 2010.

Data regarding demographics, HF etiology and severity, clinical presentation, concomitant diseases, diagnostic tests’ results, previous and current treatment and — in case of inpatients — clinical course of index hospitalization were collected in 136 European cardiology centers, including 29 centers from Poland, and entered anonymously to on-line electronic Case Report Forms.

The survey was approved by the local Ethical Review Board. All the patients included into the survey were provided with detailed information on the aim, scope and methodology of the study. Signed informed consent was obtained from each of them.

The current analysis included Polish population of Heart Failure Pilot Survey and only inpatients (i.e. patients who were admitted to hospital). In order to assess the prognostic significance of baseline RHR, patients presenting with bradyarrhythmia or ventricular tachyarrhythmia as a reason for HF decompensation and index hospitalization, were excluded from the analysis.

Study endpoints

The primary endpoint was death during index hospitalization. Secondary endpoints included duration of hospital stay, time in Intensive Cardiac-Care Unit (ICCU), need for inotropic support and diuretic treatment, and clinical status expressed as New York Heart Association (NYHA) class at hospital discharge.

Statistical analysis

Categorical data were presented as number of patients and percentages. For ordinal variables and non-normally distributed continuous variables, median value and interquartile range (IQR) were used. Type of distribution was calculated by Shapiro-Wilk test with an alpha level set at 0.05. Significance of differences between groups was determined by Fisher’s exact test for categorical variables and Mann-Whitney U test for ordinal or non-normally distributed continuous variables. To determine the risk factors of in-hospital mortality, univariate and multivariate logistic regressions were performed. In multivariate logistic regression model all factors with p values lower than 0.1 in univariate analyses were used. Statistical significance was considered for p values lower than 0.05. Statistical analyses were performed using SAS software, version 9.2.

Results

Study group selection

Out of 5,118 patients included in the Heart Failure Pilot Survey across Europe, 893 patients were enrolled in Polish centers. In the Polish population of the registry, there were 650 inpatients. Thirty patients were admitted to hospital due to ventricular tachyarrhythmia and 21 patients due to bradyarrhythmia — those patients were excluded from the analysis. Data regarding RHR at hospital admission were missing for one of the remaining patients. Therefore, the final analysis included 598 patients hospitalized due to HF.

The flow chart of patient enrollment in the study is shown in Figure 1.

Study group characteristics

Baseline characteristics of the study group are presented in Table 1. Median age in the analyzed group was 69 (IQR: 58–78) years, 386 (64.6%) patients were male. In 358 (59.9%) patients HF was assumed to have ischemic etiology and in
242 (40.5%) patients this had been previously confirmed by coronary angiography. Other causes of HF in the study group were: valvular heart disease (72 [12.0%] patients), hypertension (66 [11.0%]), dilated cardiomyopathy (59 [9.9%]) and tachycardia-induced cardiomyopathy (9 [1.5%]). In 34 (5.7%) patients the etiology of HF was not defined by investigators.

The most common reason for HF decompensation leading to index hospitalization was acute coronary syndrome (in 179 [30.0%] patients). Other triggering factors of HF decompensation leading to index hospitalization were: atrial fibrillation (AF) (103 [17.3%] patients), uncontrolled hypertension (91 [15.2%]), HF treatment non-compliance (89 [14.9%]), infection (51 [8.5%]), renal dysfunction (43 [7.2%]), anemia (29 [4.9%]), iatrogenic effect (7 [1.2%]) and “other” causes (240 [40.2%]) — with a possibility to name more than one reason of HF decompensation for each patient.

Median RHR at hospital admission was 80 (IQR: 70–100) bpm. Electrocardiogram at hospital admission was available for 576 patients, with sinus rhythm (SR) in 370 patients, AF (as the leading rhythm) in 150 patients, paced rhythm in 54 patients and “other” rhythm in 2 patients. Four hundred and two patients received beta-blockers before index hospitalization, including: carvedilol (188 patients), bisoprolol (93), metoprolol (91), sotalol (13), nebivolol (7), propranolol (5), atenolol (3) and betaxolol (2 patients). There was no distinction between metoprolol succinate and metoprolol tartrate in the Heart Failure Pilot Survey Case Report Forms. Only 39 patients (9.7% out of 402 patients) received target doses of beta-blockers recommended by the current guidelines (i.e. bisoprolol 10 mg daily, carvedilol 50 mg daily, metoprolol 200 mg daily and nebivolol 10 mg daily) [4].

Median NYHA class at admission was III (IQR: II–IV). Median left ventricular ejection fraction (LVEF) in the study group was 37% (IQR: 27–49%).

**Primary endpoint**

Twenty-one patients (3.5% of the study group) died during index hospitalization. Compared to patients who survived, patients who died were older, more often had a history of stroke or transient ischemic attack (TIA). These patients were characterized by several characteristics at admission: worse clinical presentation (higher NYHA class), higher HR, lower systolic and diastolic blood pressure, lower LVEF, lower glomerular filtration rate (GFR) and lower natrium and hemoglobin concentrations, as shown in Table 1.

In univariate analyses, factors that predicted death during index hospitalization were: higher age, a history of a previous stroke or TIA, higher NYHA class at admission, higher HR at admission, lower systolic and diastolic blood pressure at admission, lower LVEF, lower GFR and lower hemoglobin and natrium concentrations at admission. A trend was observed for previous statin treatment and acute coronary syndrome as a reason for index hospitalization. Univariate analyses are shown in Table 2.

In multivariate analysis, higher HR at admission (OR 1.594 [per 10 bpm]; 95% CI 1.061–2.395; p = 0.0248) and lower natrium concentration at admission (OR 0.767 [per 1 mmol/L]; 95% CI 0.618–0.952; p = 0.0162) were the only independent predictors of in-hospital mortality (Table 3). A trend was observed for lower LVEF (p = 0.0591) and lower hemoglobin concentrations (p = 0.0709). Due to lack of complete data for some of the patients in the registry, the multivariate analysis included only those patients (425 out of 598) for whom all required parameters were available.

We also performed additional analyses, separately for 370 patients with SR and for 150 patients with AF at hospital admission, to evaluate the impact of resting HR at admission on in-hospital mortality in those two subgroups of patients. In univariate analyses we observed a significant association between higher HR and primary endpoint.
in patients with AF (OR 1.37 [per 10 bpm]; 95% CI 1.00–1.87; p = 0.0495) and a borderline association in patients with SR (OR 1.26 [per 10 bpm]; 95% CI 0.99–1.61; p = 0.058). However, none of the predictive factors from the univariate analyses was found to be an independent risk factor in multivariate analyses. That was most probably a result of insufficient statistical power due to a very small number of events in both subgroups (4 deaths in 132 patients with complete data available for multivariate analysis in the subgroup with AF and 5 deaths in 274 patients with complete data available for multivariate analysis in the subgroup with SR).

Table 1. Baseline characteristics of patients who survived and patients who died during hospitalization. In each bar, a total number (n) of patients for whom the given variable was available in the registry is shown. Continuous and ordinal variables are shown as a median value and interquartile range (IQR).

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|-----------------|-----------------|-----------------|
| **Alive (n = 577)** | **Dead (n = 21)** | **P** |
| **Demographics** | | |
| Age [years] | 69 (58–77); n = 577 | 80 (67–84); n = 21 | 0.0036 |
| Male | 64.8% (374/577) | 57.1% (12/21) | 0.49 |
| Body mass index [kg/m²] | 27.7 (24.4–31.3), n = 514 | 26.2 (24.8–31.6), n = 14 | 0.85 |
| **Heart failure (HF)** | | |
| Ischemic etiology of HF | 59.8% (345/577) | 61.9% (13/21) | 1.0 |
| LVEF [%] | 37 (27–50), n = 510 | 27 (20–36), n = 15 | 0.0092 |
| **Medical history** | | |
| Current smoking | 55.5% (320/577) | 57.1% (12/21) | 1.0 |
| Coronary artery disease | 58.5% (337/576) | 71.4% (15/21) | 0.27 |
| Previous stroke or TIA | 9.4% (54/575) | 23.8% (5/21) | 0.046 |
| Diabetes mellitus | 35.0% (202/577) | 47.6% (10/21) | 0.25 |
| Hypertension | 66.7% (385/577) | 76.2% (16/21) | 0.47 |
| COPD | 12.9% (74/575) | 14.3% (3/21) | 0.74 |
| Chronic renal disease | 22.4% (129/576) | 38.1% (8/21) | 0.11 |
| **Previous pharmacotherapy** | | |
| Previous treatment with ACEI | 61.6% (333/541) | 63.2% (12/19) | 1.0 |
| Previous treatment with ARB | 6.9% (37/539) | 5.3% (1/19) | 1.0 |
| Previous treatment with ACEI or ARB | 1.5% (8/539) | 0.0% (0/19) | 1.0 |
| Previous treatment with beta-blockers | 72.3% (391/541) | 57.9% (11/19) | 0.19 |
| Previous treatment with aldosterone antagonists | 41.4% (224/541) | 42.1% (8/19) | 1.0 |
| Previous treatment with statin | 53.0% (287/541) | 31.6% (6/19) | 0.0997 |
| **Index hospitalization** | | |
| ACS as a cause of HF decompensation | 29.3% (169/576) | 47.6% (10/21) | 0.088 |
| HR at admission [bpm] | 80 (70–100), n = 577 | 100 (80–130), n = 21 | 0.019 |
| AF at admission | 34.1% (197/577) | 42.8% (9/21) | 0.48 |
| SBP at admission [mm Hg] | 130 (115–150), n = 576 | 110 (90–130), n = 21 | 0.001 |
| DBP at admission [mm Hg] | 80 (70–90), n = 576 | 70 (60–80), n = 21 | 0.0017 |
| NYHA class at admission | III (II–IV), n = 575 | IV (IV–IV), n = 21 | < 0.0001 |
| NYHA class I | 1.4% (8/575) | 0.0% (0/21) | |
| NYHA class II | 24.7% (142/575) | 0.0% (0/21) | |
| NYHA class III | 49.4% (284/576) | 23.8% (5/21) | |
| NYHA class IV | 24.5% (141/575) | 76.2% (16/21) | |
| Hemoglobin concentration at admission [g/dL] | 13.3 (12.1–14.6), n = 564 | 12.1 (11.0–13.7), n = 21 | 0.014 |
| GFR at admission [mL/min/1.73 m²] | 65.9 (46.2–93.3), n = 509 | 42.9 (30.3–58.3), n = 13 | 0.0192 |
| Natrium concentration at admission [mmol/L] | 138.9 (136.0–141.0), n = 568 | 135.0 (132.9–138.8), n = 21 | 0.0052 |

HF — heart failure; LVEF — left ventricular ejection fraction; TIA — transient ischemic attack; COPD — chronic obstructive pulmonary disease; ACEI — angiotensin-converting-enzyme inhibitor; ARB — angiotensin receptor blocker; ACS — acute coronary syndrome; HR — heart rate; AF — atrial fibrillation; SBP — systolic blood pressure; DBP — diastolic blood pressure; NYHA — New York Heart Association; GFR — glomerular filtration rate
Secondary endpoints

Median duration of hospital stay was 7 (IQR: 4–11) days, and median time spent in ICCU was 1 (IQR: 0–5) day. Sixty-two (10.4%) patients required inotropic support and 469 (78.4%) patients received diuretic treatment. Median NYHA class at discharge was II (IQR: II–III).

In univariate analyses, higher HR at hospital admission was associated with a more frequent use of inotropic support (p = 0.0462; OR [per 10 bpm] 1.115; 95% CI 1.002–1.241) and diuretics (p = 0.0426; OR [per 10 bpm] 1.104; 95% CI 1.003–1.215), worse clinical status (higher NYHA class) at discharge (p = 0.0483; r = 0.0819), and longer hospital stay (p = 0.0303; r = 0.0894). There was no relation between HR and time in ICCU (p = 0.1644).

Discussion

In the Polish population of patients hospitalized for HF, RHR at admission was found to be a predictor of in-hospital mortality, independently of other markers of the severity of HF decompensation, such as blood pressure and clinical status (NYHA class) at admission. An increase in HR of 10 bpm was followed by an almost 60% increase
in the risk of death during hospitalization. The analysis included patients with SR, as well as patients with AF (as the leading rhythm) and patients with paced rhythm at hospital admission. Separate analyses of subgroups with SR and AF at hospital admission yielded equivocal results due to insufficient statistical power.

RHR at admission was also associated with worse clinical course during index hospitalization, with a more frequent need for inotropic support and diuretic treatment, worse clinical status at hospital discharge and longer hospital stay in univariate analyses. However, these associations were weak, as Spearman’s rank correlation coefficient (r) for relationship of HR with NYHA class and hospital stay were below 0.1.

Raised RHR is a known risk factor for unfavorable outcome in HF. This was most evidently demonstrated in the SHIFT trial, which randomized 6,558 patients with chronic, symptomatic HF, stable on current medication, with LVEF of 35% or lower, SR and resting HR over 70 bpm to ivabradine or placebo. After a median follow-up for almost 2 years, an 18% risk reduction in primary endpoint (cardiovascular death or hospital admission for worsening HF) was observed for patients allocated to ivabradine group [5]. A post-hoc analysis demonstrated that this effect was completely attributable to HR reduction on ivabradine therapy, as treatment results were neutralized after adjustment for change of HR at 28 days. In patients receiving placebo, baseline RHR over 87 bpm was associated with more than 2-fold higher risk for primary endpoint than baseline HR below 72 bpm [3]. Unlike the SHIFT trial, our study included patients with decompensated HF rather than stable chronic HF, irrespective of LVEF, with both, SR and AF, and focused on short-term prognosis.

A recent post-hoc analysis of another large, randomized clinical trial — Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) delivered results similar to conclusions from the SHIFT trial [6]. In a cohort of 7,599 patients with chronic, symptomatic HF, baseline HR in the highest tertile (with median HR of 85 bpm) was associated with a significantly higher risk of cardiovascular death and HF hospitalization after 38 months compared with the lowest HR tertile (with median HR of 60 bpm). The relationship between HR and outcomes was similar in patients with LVEF below and over 40%. However, baseline HR had no predictive value in patients with AF [6].

A few other small, prospective, observational studies confirmed significance of RHR for prognosis in chronic HF [7, 8]. Interestingly, higher HR correlated with increased risk of arrhythmic events in patients with dilated cardiomyopathy and an implantable cardioverter-defibrillator [9].

Baseline HR at hospital admission was also found to influence outcome in patients with acute, decompensated HF. Recently, three independent risk scores assessing short-term prognosis in patients with acute HF have been developed [10–12]. All these three predictive models were derived from data from large cohorts of patients admitted for acute HF (including 7,433; 2,015 and 5,306 patients) and stratified the risk of death at 7
days, death or HF worsening at 7 days, and death at
30 days, respectively. In all these studies, baseline HR
turned out to be an independent prognostic factor
and was incorporated in risk stratification models,
together with other predictive factors, including age,
comorbid conditions, baseline laboratory findings and other presenting clinical features, such as systolic blood pressure. However, contrary to our study, none of these three studies included LVEF in the multivariate analysis [10–12].

The association between HR and prognosis in HF might partially explain the beneficial effect of beta-blockers in HF patients. Guidelines recommend that patients with HF receive beta-blockers in doses used in the trials that have proven their efficacy [4]. However, a meta-analysis of 23 prospective, randomized, placebo-controlled trials with beta-blockers, including over 19,000 patients with HF, revealed significant impact of achieved HR reduction on all-cause mortality, with no relationship between mortality and beta-blockers dosing. Every HR reduction of 5 bpm with beta-blocker treatment was followed by an 18% reduction in the risk of death [13]. Another study, including 421 hospitalized HF patients, demonstrated that not the discharge HR itself, but the extent of HR reduction achieved during treatment with beta-blockers determines the risk of future cardiac events [14].

The second independent predictor of in-hospital mortality in our analysis was lower natrium concentrations. Hyponatremia is frequently observed in patients with severe HF. Data from registries and randomized controlled trials indicate that 12–27% of patients admitted to hospital for HF are hyponatremic [15–19]. In HF, hyponatremia is believed to result from increased concentrations of antidiuretic hormone (ADH, vasopressin), the secretion of which is stimulated by reduced systemic arterial blood pressure due to a low cardiac output, even in patients with volume overload and fluid retention. Long-term therapy with loop diuretics may aggravate hyponatremia [20].

Hyponatremia had previously been associated with unfavorable prognosis in HF. In observational studies, registries and post-hoc analyses of randomized clinical trials, it was reported to correlate with all-cause and cardiac mortality (both in-hospital and long-term) as well as with the risk of re-hospitalization for HF [12, 15–19, 21–23].

So far, it is not clear whether hyponatremia itself deteriorates clinical outcome in HF or whether it is merely a marker of severity of HF or other comorbid conditions [20]. Interestingly, despite a proven relationship between hyponatremia and prognosis in HF, treatment with ADH receptor antagonists, such as tolvaptan, had no impact on mortality in HF [24]. Observational studies evaluating changes in plasma natrium in patients hospitalized for HF have brought conflicting results, with some evidence that correction of hyponatremia might lead to improvement in outcome [15, 18, 25–27].

In our study, in the multivariate analysis of independent predictors of in-hospital mortality we also observed a trend for lower LVEF and lower hemoglobin concentrations at admission. Both of these variables are known prognostic factors in HF patients [12, 21–23, 28–30]. It seems possible that due to a relatively small number of events these factors did not reach statistical significance in our analysis. In a cohort of 48,612 patients hospitalized for HF and enrolled in the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry independent predictors of in-hospital mortality included i.a. resting HR, natrium concentrations and presence of left ventricular systolic dysfunction [21].

Limitations of the study

The limitations of our study result from the type of data we analyzed. The advantage of registries is that they include a broad, diverse, real-life spectrum of patients, rather than a narrow, carefully selected patient subgroup as in clinical trials. However, important drawbacks of registries are: their retrospective and observational character, simplifications necessary for data unification for analysis, limited number of data collected, as well as incompleteness of the data. In our study data of 425 (71%) out of 598 patients were complete and available for multivariate analysis. Furthermore, some potentially important variables, such as concentrations of B-type natriuretic peptide, were not available for analysis.

Conclusions

In Polish patients hospitalized for HF, higher HR at hospital admission was associated with increased in-hospital mortality.

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