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Low systolic blood pressure and high resting heart rate as predictors of outcome in patients with peripartum cardiomyopathy

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ABSTRACT

Background: Patients with peripartum cardiomyopathy (PPCM) present with low blood pressure (SBP) often preventing uptitration of heart failure medication. We aimed to study prediction of risk and the contribution of high resting heart rate (HR) and low SBP to risk in recent onset of PPCM.
Methods: Clinical assessment with HR and SBP, echocardiography and laboratory results were obtained at baseline and at six months on 206 patients with recent onset PPCM enrolled at two tertiary care centers in South Africa. Poor outcome was defined as the combined endpoint of death, LVEF < 35% or remaining in New York Heart Association (NYHA) functional class III/IV at six months. Complete LV recovery was defined as LVEF ≥ 55% at six months.
Results: Poor outcome was observed in 110 of 220 patients (53%), with 26 patients dying at six months (12.6%). There were 98 (47.5%) patients with SBP ≤ 110 mm Hg. Patients with high HR (HR ≥ 100) and low SBP (<110 mm Hg) tended to have worse outcomes than patients below the HR median and high SBP. PPCM patients with low SBP and high HR were less likely to be on ACE-inhibitors (n = 35, 69% *versus* n = 129, 84%, $p = 0.024$) and on the beta blocker carvedilol (n = 24, 47% *versus* n = 98, 64%, $p = 0.047$). Low SBP, high HR and left ventricular end diastolic diameter at baseline were predictors of poor outcome. Patients with low SBP and high HR had the highest mortality ($p = 0.0023$).
Conclusions: These findings suggest increased risk in patients with PPCM presenting with low SBP and high HR on standard heart failure medication possibly having implications on HF management.

1. Introduction

Peripartum cardiomyopathy (PPCM) is a potentially life-threatening disease that occurs in women of child-bearing age [1,2]. This disease is characterized by new onset of heart failure between several months before and six months after delivery in previously healthy women [3]. Although PPCM patients have a higher rate of spontaneous recovery of left ventricular (LV) function compared to patients with other forms of non-ischemic cardiomyopathy, normalization of LV function at six months has been reported to occur in only 23–54% of patients [5,6]. Heart rate (HR) is a risk marker for cardiovascular outcomes in hypertension [7], high cardiovascular risk after myocardial infarction and stroke [8], coronary artery disease [8] after myocardial infarction [9] and heart failure with impaired [10] or preserved [11] ejection fraction. Reduction of heart rate in patients with heart failure due to ischemic and idiopathic cardiomyopathy with the f-channel inhibitor ivabradine has been shown to improve cardiovascular outcomes [12,13]. Low systolic blood pressure (SBP) (<120 mm Hg) is common in heart failure (15–25% of patients) and is associated with increased post discharge mortality and morbidity [14–18]. Patients with PPCM often present with hypotension (<110 mm Hg, [4,6]) accompanied with very dilated hearts with poor contractility not allowing up-titration with beta blockers and ACE-inhibitors to the doses recommended by current guidelines [19]. On the other hand, physicians struggle to reduce HR to less than 80 bpm on doses of heart failure medication prescribed without accepting major side effects such as profound dizziness and fatigue. We determined the effect of HR and SBP on risk in 206 patients on tolerated heart failure medication with newly diagnosed PPCM, managed by cardiologists at tertiary care centers on six months' outcome on stable medication irrespective of other predictors of poor outcome such as left ventricular diameter and function.

2. Methods

2.1. Study design and patient recruitment

Patients were consecutively collected and managed at two tertiary care centers in South Africa: Chris Hani Baragwanath (CHB) Hospital, Soweto, and Groote Schuur Hospital, Cape Town, South Africa. Patients

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were referred from local clinics, secondary hospitals, and the Department of Obstetrics. History of pre-existing cardiac signs or symptoms, pre-eclampsia or eclampsia and mode of delivery were obtained from the patient and confirmed by examining the obstetric card carried by each patient. Signs and symptoms were recorded during first presentation at the cardiac units (baseline) and after a follow-up period of six months. Most of the patients were seen monthly (data not presented). Clinical assessment and echocardiography were performed at baseline and at six months.

Inclusion criteria were: 1) age ≥ 16 and ≤45 years; 2) symptoms of congestive heart failure that developed in the last month of pregnancy or during the first six months postpartum; 3) no other identifiable cause for heart failure; 4) LVEF ≤ 45% by transthoracic echocardiography corresponding to standard measurements; and 5) sinus rhythm. Exclusion criteria were: 1) significant organic valvular heart disease; 2) significant hypertension defined as systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg; 3) clinical conditions other than cardiomyopathy that could increase plasma levels of inflammatory markers; 4) severe anemia (hemoglobin < 9 g/dL); and 5) any clinical condition that, according to the investigators, precluded inclusion in the study, such as ischemic heart disease or malignancy. Patients were given treatment by the treating cardiologists, based on standard criteria and clinical judgment, which included ACE inhibitor, carvedilol, spironolactone and digoxin. Doses were titrated upward as tolerated throughout the first month of the study period and kept stable afterwards for the duration of the six month study period/follow-up period. Furosemide dose was titrated upward or downward as indicated according to clinical assessment over the six month period. This study was approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand, Johannesburg, South Africa and the University of Cape Town and complies with the Declaration of Helsinki. All study participants gave written informed consent before study entry.

2.2. Echocardiography, assessment of New York Heart Association functional class and noninvasive blood pressure measurements

Two-dimensional and targeted M-mode echocardiography with Doppler color flow mapping were performed using either a Hewlett Packard Sonos 5500 (Royal Philips Electronics, Amsterdam, Netherlands) or a VIVID i (General Electric Company, Fairfield, Connecticut, USA) echocardiography machine. Systolic and diastolic LV dimensions were measured according to the American Society of Echocardiography (ASE) Guidelines. Measurements of LV dimensions and function were determined using the average of ≥3 cycles. Echocardiography was taped on video or CD and stored for further reference and audit purposes.

New York Heart Association (NYHA) functional class of each patient at baseline and follow-up visits was evaluated by a physician who was provided with clinical data but blinded to the protocol and unaware of the results of the laboratory tests. BP and HR were measured noninvasively with a Critikon Dinamap vital signs monitor 1846 and calculated as mean values from five readings. Measurements were made after a 30-minute resting period in sitting position with two-minute intervals between successive measurements.

2.3. Outcomes

To assess the effect of baseline SBP and HR on outcome the patient population was divided by medians of SBP < 110 mm Hg (L), and SBP ≥ 110 mm Hg. To evaluate the relationship of SBP and HR, the PPCM patients were subdivided according to median of resting HR < 100 bpm and HR ≥ 100 bpm. Poor outcome was defined as the combined endpoint of death, LVEF < 35% or remaining in NYHA functional class III/IV at six months. Complete LV recovery was defined as an improvement to LVEF ≥ 55% at six months.

2.4. Statistics

Database management and statistical analyses were performed with SAS software, version 9.2, a statistical program (SAS Institute Inc., Cary, North Carolina, USA). Continuous data are expressed as mean ± SD or median (interquartile range, IQR). Comparison of means and proportions between groups at baseline was performed by independent *t*-test and Chi-square statistics or Fisher exact test, respectively. A Wilcoxon rank-sum test was used where data were not normally distributed. Differences of class variables and continuous data between baseline and six months were assessed by a McNemar test and a paired *t*-test or sign test (data not normally distributed), respectively. Univariate and stepwise multiple logistic regression analyses were performed to establish independent predictors of poor outcome and LV recovery with blood pressure, and echocardiographic parameters after adjusting for age, BMI, EF, NYHA and LVEDD. Kaplan and Meier analyses was used to establish the contribution of SBP (LSBP *vs.* HSBP) and HR (HHR *vs.* LHR) separately on mortality. Log-rank tests were used to compare the survival curves between the two and the 4 strata (LSBP *vs.* HSBP, HHR *vs.* LHR); (HHR-LSBP, HHR-HSBP, LHR-HSBB and LHR-LSBP) respectively. Significance was assumed at a two-sided value of $p < 0.05$.

3. Results

3.1. Study group

Two hundred and six consenting consecutive patients diagnosed with PPCM and fulfilling the inclusion criteria were enrolled in the study. All women were of African descent. Baseline clinical characteristics are listed in Table 1. Notably, the mean age was 30.6 ± 6.8 years, median parity was 2 (range, 0–7), mean BMI was 25.8 ± 5.3 kg/m^2 and most of the women (78%) presented with NYHA functional class III or IV symptoms.

Among the 206 patients included in the study, 187 (91%) received treatment with furosemide (median dose = 160 mg), 164 (80%) were treated with an angiotensin-converting enzyme inhibitor (median dose enalapril = 10 mg), and 119 (59%) patients received digoxin (mean dose 0.25). Carvedilol (the only used beta blocker in this population) was initiated in 122 (59%) patients after resolution of overt heart failure (median dose = 12.5 mg). Patients above and below the median of SBP (110 mm Hg) and HR (100 bpm) at baseline were studied. Patients with an LVEF < 25% or LV thrombus were treated with warfarin.

Ninety eight of the patients (47.5%) had a low SBP (L SBP) (SBP < 110 mm Hg). The clinical characteristics are listed in Table 2. PPCM patients with L SBP had lower BMI compared to the rest of the patients (24.5 ± 4.5 kg/m^2 *vs.* 26.7 ± 5.6, $p = 0.003$), but no statistically significant differences were found regarding other baseline characteristics (Table 2). No differences between dosage levels or in the number of PPCM patients taking ACE-inhibitors, carvedilol or diuretics were shown between patients with L SBP in comparison to patients with normal or higher SBP.

Patients with high HR (H HR ≥ 100 bpm) were less likely to be on ACE-inhibitors (n = 75, 72%, *versus* n = 90; 90%) in the low (*i.e.*, <100 bpm) HR group ($p = 0.006$, Table 3). However, the median doses of ACE-inhibitors, carvedilol or diuretics were similar in both groups.

Among the cohort of PPCM patients 51 women (25%) presented L SBP and H HR. These 51 PPCM patients were less likely to be on ACE-inhibitors (n = 35, 69% *versus* n = 129, 84%, $p = 0.024$) and on carvedilol (n = 24, 47% *versus* n = 98, 64%, $p = 0.047$) compared to the rest of the study sample. Median dosages did not differ between both groups of patients (not shown).

3.2. Characteristics among survivors at six months

Table 4 lists the characteristics of the survivors (n = 141) compared to nonsurvivors among the study population at baseline and six months. Mean LV end systolic dimension (LVESD) decreased significantly from