Central Chemoreflex Sensitivity and Parasympathetic Nervous Activity in patients with Heart Failure

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Abstract—Although some studies point towards exacerbated central chemoreflex sensitivity (CCS) and reduced parasympathetic nervous activity (PNA) in patients with heart failure (HF), others dispute this finding by indicating their unchanging condition. The aim of this study is to compare CCS and PNA between patients with HF and healthy individuals. Eighteen patients with HF and 14 healthy individuals participated in the study. CCS was assessed through 7% CO₂ rebreathing test for 4 minutes. PNA was determined based on Fast Fourier Transformation using the high-frequency component of heart rate variability. CCS was not different between HF patients [MD: 0.83 (0.49 to 1.54) l.min.mmHg] and healthy individuals [MD: 0.88 (0.16 to 2.56) l.min.mmHg]. PNA in HF patients [MD: 288 (266 to 1188) ms] also did not differ from healthy individuals [MD: 299 (81 to 1099) ms]. In conclusion, HF patients subjected to adequate clinical management may present preservation of CCS and PNA.

Keywords—Central chemoreflex sensitivity, vagal modulation of heart rate, heart failure, autonomic control.

I. INTRODUCTION

Heart Failure (HF) is a complex clinical syndrome in which the heart becomes unable to effectively pump blood due to functional and anatomical cardiac impairment [1,2]. Over time, it can lead to several electrophysiological changes, as well as to changes in respiratory and cardiac control reflexes [3] such as chemoreflex sensitivity and parasympathetic nervous activity [4,5].

Exacerbated central chemoreflex sensitivity (CCS) is a pathophysiological change often attributed to HF [4]. It leads to chronic sympathetic nervous system overactivation and to reduced parasympathetic nervous activity (PNA) [5], which favors disease progression and worsened prognosis [6]. Thus, it results in increased cardiac arrhythmia and heart failure-associated mortality rates [7].

Although some studies point towards exacerbated CCS in HF patients [1,7,8,9] others contradict this finding by suggesting that CCS and the parasympathetic nervous activity remain unchanged [10] Based on these divergent findings and on the clinical importance given to these data, the aim of the present study was to compare CCS and parasympathetic nervous activity between HF patients and healthy individuals.

II. METHODS

2.1 Sample

HF patients were screened based on echocardiographic examinations performed at local reference centers in cities located in Rio Grande do Sul State, Brazil, from 2014 to 2018. Eighteen (18) HF patients and 14 healthy individuals, who were matched by sex and age group, participated in the study. Inclusion criteria comprised clinically stable HF patients, who are classified as NYHA functional classes I, II and III, and whose medication had not been changed in the previous 3 months. Patients presenting unstable angina, atrial fibrillation, acute myocardial infarction or recent cardiac surgery (< 6 months), severe obesity, smoking habit, and spirometry-
assessed chronic obstructive pulmonary disease were excluded from the study [25]. Healthy and physically active individuals reporting smoking habit were also excluded from the study. All participants signed the Informed Consent Form. The study was approved by the local Research Ethics Committee.

2.2 Study Protocol

The CCS and parasympathetic nervous activity assessment protocol was performed in the morning, in a room with controlled temperature (22°C). All individuals were instructed to fast, to avoid caffeinated and alcoholic beverages for at least 10 hours before the test and to not exercise for at least 48 hours.

CCS was evaluated based on the CO₂ rebreathing technique [26]. After participants were left to rest in sitting position for 15 minutes, they were connected to a system, which consisted of a spirometer coupled to bacteriological and oral filter. The inspiratory pathway was connected to a trachea with three-way valve in order to allow participants to breathe ambient air or gas coming from a 30-liter balloon. Volunteers subjected to the protocol used nasal clip. Initially, 5 basal minutes were recorded and, then, participants inhaled a mixture of CO₂ (7%) and O₂ (93%), for 4 minutes. CCS was based on the ratio between minute ventilation (MV) and partial end-tidal CO₂ pressure (PetCO₂), which was calculated through linear regression analysis and expressed in liters per minute per mmHg (l.min.mmHg).

PNA was evaluated after participants had rested in supine position for 15 minutes. Individuals were connected to a system composed of a spirometer coupled to bacteriological and oral filter. They used nasal clip and were instructed to perform 15 controlled breathings per minute, which were guided by the sound of a metronome for 10 minutes. PNA was obtained through spectral analysis by applying the Fast Fourier Transform algorithm over 5-minute segments. The low frequency component (0.04 - 0.15 Hz), representative of sympathetic and parasympathetic nervous activity and the high frequency component (0.15 -0.45 Hz), representative of parasympathetic nervous activity, were expressed in ms [27].

2.3 Variables

Respiratory flow was assessed in a spirometer (FE141 spirometer, ADInstruments, Sydney Australia, 1000-liter flow head) calibrated with a 3-liter syringe. Respiratory rate (RR) and tidal volume (TV) were determined through the respiratory flow channel. Minute ventilation was calculated in additional channel by multiplying the RR (breathing/min) by the tidal volume [28]. HR was noninvasively measured beat by beat (ADInstruments, bioamp ML132, Australia). PetCO₂ was measured in a capnograph (CO₂ gas Analyzer-17630, Vacumed, Silver Edition, USA). Systolic (SBP) and diastolic (DBP) blood pressures were measured in mercury sphygmomanometer (Unitec®, Brazil), which was placed on participants’ dominant arm along with a stethoscope (Rappaport Premium). Arterial oxygen saturation (SatO₂) was measured with a pulse oximeter (CONTEC CMS50C) positioned on participants’ middle finger. The PowerLab system [Powerlab / 16SP ML880, AD Instruments (ADI A, USA] was used to collect data, which were analyzed in the LabChart Pro V.8 software, ADInstruments.

2.4 Statistical analysis

Data presenting normal distribution were expressed as mean and standard deviation. Student’s t-test for independent samples was used to compare normal distribution variables between groups. CCS and PNA data did not present normal distribution, so they were expressed as median and confidence interval. Mann-Whitney test was used to compare these two variables between groups. Two-way analysis of variance (ANOVA) was used to evaluate respiratory and hemodynamic responses during CCS assessment, since they recorded normal distribution. P ≤ 0.05 was considered significant.

III. RESULTS

Table 1 shows the characteristics of healthy individuals and HF patients. One HF patient was classified as NYHA functional class III (moderate symptoms), eight HF patients were classified as functional class II (mild symptoms) and nine of them were at functional class I (no symptoms) [11]. The low and the high frequency component of HR variability in HF patients did not differ from healthy individuals.

HF patients presented CCS: 0.83 (0.49 to 1.54) l.min.mmHg, whereas healthy individuals presented CCS: 0.88 (0.16 to 2.56) l.min.mmHg; there was not significant difference between groups (P = 1.00).

Table 1. Participants’ characteristics

|          | HF (n=18) | HS (n=14) | P      |
|----------|-----------|-----------|--------|
| Sex      | 12 men / 6 women | 9 men / 5 women | -      |
| Age (years) | 57 ± 7 | 57 ± 6 | 0.95   |
| Weight (kg)  | 80 ± 15 | 72 ±10 | 0.41   |
Table 2 shows that the central chemoreflex progressive increases MV in HF patients and healthy subjects. PetCO₂ presented similar increase between HF patients and healthy subjects at all times in comparison to baseline values. HR increase at the 3rd and 4th minutes was similar in both groups in comparison to baseline values. HR increase was similar in both groups from the 2nd minute on. SBP and SatO₂ increase in all CO₂ administration minutes, and DBP increase from the 2nd minute on, were similar in both groups in comparison to baseline values (Table 2).

| Group | Baseline | 1 min | 2 min | 3 min | 4 min |
|-------|----------|-------|-------|-------|-------|
| HF    | 24       | 29    | 35    | 37    | 40    |
| MV    | 22       | 26    | 30    | 34    | 38    |
| PetCO₂| 48       | 52    | 55    | 55    | 55    |

Data expressed as mean and standard deviation.

CCS: central chemoreflex sensitivity; HR: heart failure; HS: healthy subjects. ANOVA: MV (minute ventilation): time = 0.001; group = 0.549; time*group = 0.855; PetCO₂ (partial end-tidal CO₂ pressure): time = 0.001; group = 0.038; time*group = 0.573; RR (respiratory rate): time = 0.003; group = 0.187; time*group = 0.574; HR (Heart Rate): time = 0.001; group = 0.071; time*group = 0.224; SBP (systolic blood pressure): time = 0.001; group = 0.326; time*group = 0.056; DBP (diastolic blood pressure): time = 0.001; group = 0.540; time*group = 0.969; SatO₂ (peripheral oxygen saturation): time = 0.001; group = 0.303; time*group = 0.149.

* p <0.05 in comparison to baseline value.

IV. DISCUSSION

The current study has shown that the CCS of HF patients does not differ from that of healthy individuals.
CCS preservation in HF patients could explain the preserved PNA recorded in our study, a fact that could contribute to improve the survival prognosis of these individuals.

Our findings about CCS preservation in HF patients in comparison to such preservation in healthy individuals are in compliance with previous studies conducted by Paleczny et al. (2017) and Contini et al. (2013). According to these studies, patients presented low-severity symptoms and most of them were classified as NYHA I and II. The low CCS severity recorded for HF patients assessed in the aforementioned studies, and in the present research, could explain the CCS preservation.

In addition, the use of beta-blocker drugs could influence the chemoreflex sensitivity response. Paleczny et al. (2017) found unchanged CCS in HF patients treated with beta-blockers and ACE-I. These findings may explain, at least in part, the findings in the present study, since 88% of the assessed individuals used beta-blockers. According to Contini et al. (2013), beta-blockers with different pharmacological characteristics (drug-blocked receptor type) have different effects on CCS - Carvedilol is the most effective drug in reducing CCS and peripheral chemoreflex sensitivity, since it improves ventilation efficiency during exercise sessions. According to Toledo et al. (2017), the use of propranolol (beta-blocker) in animal models also eliminated the deleterious effects of CCS overactivation, such as autonomic dysfunction and cardiac arrhythmia.

The use of beta-blockers could also explain the preserved PNA found in HF patients than in healthy individuals. These drugs presented antagonistic action to sympathetic activation, restored cardiac and circulatory reflex control, attenuated vasoconstrictor neurohumoral systems and improved myocardial performance by reducing individuals’ heart rate and oxygen demand.

Although some studies have recorded exacerbated CCS, the prevalence of this finding was not high in all studies. Mirizzi et al. (2016) have found CCS exacerbation in 56% of patients. However, these patients were older, presented lower LVEF, larger right ventricular diameter and worse ventilatory efficiency than the ones assessed in the present study. Giannoni et al. (2008) found increased CCS in only 20% of patients who presented the worst clinical severity. On the other hand, Giannoni et al. (2009) found CCS exacerbation in 23% of HF patients who have presented low functional capacity, low parasympathetic nervous activity, as well as high prevalence of paroxysmal atrial fibrillation and ventricular tachycardia.

Accordingly, findings in the present study may have been influenced by the exclusion of patients with atrial fibrillation, since previous studies have shown that patients with chemoreflex exacerbation have higher prevalence of atrial fibrillation, as well as that atrial fibrillation in HF patients may be associated with reduced vagal modulation of HR, which leads to increased cardiac arrhythmic events and heart failure-associated mortality rates.

According to the meta-analysis conducted by Pearson & Smart (2018), PNA was predominant or improved in HF patients who underwent, or started, physical exercises of several modalities such as weight training, aerobics, inspiratory muscle training and yoga, among others. Prospective long-term cohort study with 256 HF patients reinforces that the severity of inspiratory muscle weakness, and shorter walking distance, by 6-minutes walk distance test, proportionally increases mortality risk, but this outcome is more accurately discriminated by the maximal inspiratory pressure.

However, patients assessed in the present study were physically inactive, and it corroborates the idea that adequate clinical management based on the use of beta-blockers, and the clinical stability provided by these drugs, represent a protective effect according to the vagal modulation perspective.

The CCS and PNA preservation in HF patients assessed in the present study suggests better prognosis for them, since increased chemoreflex sensitivity can cause peripheral vasoconstriction and lead to clinical HF worsening [16] exacerbate dyspnea symptoms and exercise-related fatigue [23] as well as increase the risk of cardiac events with reduced survival rates.

Thus, the adequate clinical management based on beta-blockers, the exclusion of individuals with atrial fibrillation, the low disease severity and the clinical stability of HF patients assessed in the present study may have contributed to preserve both CCS and the PNA.

According to a recent study, the preservation, or not, of the PNA in optimally treated HF patients did not show differences in survival rates in a 5-year follow-up. Although CCS preservation did not show prognostic survival implications in a previous study with a 15-month follow-up it is necessary conducting a long-term research on the prognostic and clinical implications on the chemoreflex sensitivity of patients subjected to optimal clinical management.
V. CONCLUSION
Heart failure patients may present central chemoreflex sensitivity preservation, and even increased parasympathetic nervous activity, due to appropriate clinical management. The impact of these findings on patients’ survival should be investigated in long-term cohort studies.

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