Autonomic Function and Cardiorespiratory Coupling Analysis in Patients with Chronic Heart Failure with Reduced and Preserved Ejection Fractions

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Abstract

Chronic heart failure (CHF) is a syndrome in which the heart fails to pump enough blood to meet the body's needs. It is classified into two phenotypes: CHF with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF). CHF disrupts autonomic control and cardiorespiratory coupling (CRC). CRC quantifies the dynamic interactions between heart period (HP) and respiration (RESP). The assessment of CRC offers insights beyond traditional univariate markers, such as the high frequency (HF, 0.15-0.5 Hz) power of HP variability (HFa_{HP}) and the power of variability of the time interval between Q-wave onset and T-wave end (QT) in the low frequency (LF) band (LFa_{QT}). In this study, we analyzed HFa_{HP}, LFa_{QT}, and CRC strength in 29 subjects belonging to three gender-balanced groups (HFrEF: n=10, 62±11 yrs; HFpEF: n=9, 56±14 yrs; CTRL: n=10, 58±9 yrs). CRC was estimated via K^2 between RESP on HP at the respiratory rate. Compared to HFrEF in the HFpEF group, K^2 and HFaHP were reduced (0.80±0.16 vs 0.46±0.22 and 158±80 ms^2 vs 113±94 ms^2 respectively) and LFaQT was increased (48±55 ms^2 vs 143±109 ms^2). Markers in CRTL group were more similar to HFrEF. These results suggest compensatory autonomic mechanisms that help maintain proper cardiac function, with these responses depending on the CHF phenotype.

1. Introduction

Chronic heart failure (CHF) remains a leading cause of cardiovascular morbidity and mortality worldwide. CHF is a complex, multifactorial clinical syndrome characterized by structural and/or functional cardiac abnormalities that impair the heart's ability to fill or eject blood efficiently, resulting in inadequate tissue perfusion. Its pathophysiology involves diverse mechanisms and evolves with the state of the myocardium [1].

CHF patients are categorized according to left ventricular ejection fraction (EF) as having reduced EF (HFrEF) when EF is below 40%, and CHF with preserved EF (HFpEF) when EF is above 50%. Subjects with HFrEF, the left ventricle becomes dilated and weakened, resulting in a pressure-volume profile characterized by decreased stroke volume, elevated end-diastolic pressure, and increased end-diastolic volume. Conversely, individuals with HFpEF typically involves ventricular hypertrophy and impaired relaxation, with the pressure-volume relationship showing elevated end-diastolic pressure, but reduced stroke volume and end-diastolic volume [1].

Stimulation of the sympathetic adrenergic system, accompanied by suppression of parasympathetic cardiac modulation, serves as a key compensatory mechanism that temporarily supports stroke volume by enhancing ventricular contractility despite impaired myocardial function. Given the key role of autonomic regulation in CHF progression, there has been growing interest in non-invasive methods to assess cardiac autonomic control. Traditional markers derived from the spontaneous fluctuations of heart period (HP) and the time interval between Q-wave onset and T-wave end (QT), have been extensively employed to assess autonomic control in CHF patients [2]. However, these indexes are notably influenced by respiratory frequency, particularly in the case of respiratory sinus arrhythmia, emphasizing the need to incorporate respiratory signals in the analysis. Conventional univariate approaches may have limited capacity in characterizing complex interactions between

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heart and respiratory system [3]. Therefore, the study of the network between cardiac and respiratory activities via cardiorespiratory coupling (CRC), has emerged as a valuable complementary tool for assessing the integration of cardiac and respiratory regulations [4]. In patients with type 2 *diabetes mellitus*, CRC offered insight into the integrated autonomic and respiratory controls and may detect dysfunction earlier than conventional markers [5]. In CHF patients, higher CRC have been associated with better exercise capacity, which might be related to better efficiency in oxygen distribution and carbon dioxide removal [6].

Despite its significant role in HFrEF and HFpEF patients, CRC has not been investigated yet. Thus, this study aims to evaluate the CRC and traditional autonomic markers in CHF patients across varying EF levels.

2. Experimental Protocol and Data Analysis

2.1. Experimental Protocol

Participant characteristics are summarized in Table 1. Data were collected from 19 patients diagnosed with CHF, categorized into HFrEF (n=10) and HFpEF (n=9). All patients underwent cardiopulmonary exercise testing (CPET) as part of a clinical evaluation at IRCCS Policlinico San Donato, San Donato Milanese, Italy. Additionally, a control group (CTRL) consisting of 10 individuals without a diagnosis of CHF was included in this study. During data collection, participants remained seated and at rest, breathing spontaneously, while simultaneous 12-leads electrocardiogram (ECG) and respiratory flow (RF) signals were recorded at a sampling rate of 500 Hz. These measurements were obtained for a duration of 3 to 5 minutes. The study protocol was reviewed and approved by the ethics committee of San Raffaele Hospital in Milan, Italy. All procedures complied with the Declaration of Helsinki, and written informed consent was obtained from each participant prior to enrollment.

Table 1. Population characteristics.

Variable	HFrEF (n=10)	HFpEF (n=9)	CTRL (n=10)
age [yrs]	62 ± 11	56 ± 14	58 ± 9
sex [m/f]	6/4	7/2	6/4
SBP [mmHg]	129 ± 17	127 ± 10	126 ± 10
DBP [mmHg]	76 ± 7	79 ± 3	76 ± 6
VO_2peak [$mL \cdot kg^{-1} \cdot min^{-1}$]	16 ± 4	16 ± 5	28 ± 7*
beta-blockers [%]	8 (80)	7 (77)	0
BMI [$kg \cdot m^{-2}$]	28 ± 3	30 ± 5	26 ± 8

CHF=chronic heart failure; EF=left ventricular ejection fraction; HFpEF=CHF with preserved EF; HFrEF=CHF with reduced EF; CTRL=control group; SBP=systolic blood pressure; DBP=diastolic blood pressure; VO_2peak=peak oxygen consumption; BMI=body mass index. The symbol * indicates $p<0.05$ CTRL vs HFpEF or vs HPrEF.

2.2. Variability Series Extraction

ECG traces were analyzed using a custom-built software application, previously described in the literature [7]. This software automatically identified HP and QT interval. Detection of the R-wave peak was performed using a threshold applied to the first derivative of the ECG signal, followed by parabolic interpolation to enhance temporal precision. HP was defined as the interval between two consecutive R-wave peaks, while the *n*th QT interval was estimated as the duration between the R-wave peak and the end of the T-wave following the *n*th HP [8]. The offset of the T-wave was identified automatically as the point on its descending limb where the absolute value of the first derivative fell below 30% of the maximum absolute slope of the T-wave. Abnormal T-wave morphologies, such as biphasic shapes, were not observed. Stationary sequences of 200 consecutive HP and QT intervals were selected for the analysis. The respiratory flow (RF) signal was sampled at the beginning of the *n*th HP to derive the respiratory (RESP) series, with values reported in $mL \cdot s^{-1}$.

2.3. HP and QT Variability Analysis

Mean and variance of the HP series (μ_{HP} and σ^2_{HP}) were computed and expressed in ms and ms^2 respectively. Respiratory rate was derived from the RESP series. After linear detrending, HP and QT variability series were analyzed in the frequency domain via a parametric approach based on the autoregressive model with optimization of the model order. The resulting power spectral density was decomposed into components categorized according to frequency bands. As to the QT variability we computed the power in the low-frequency (LF) band from 0.04 to 0.15 Hz (LFa_{QT}), while in the case of HP variability we calculated the power in the high frequency (HF) band from 0.15 to 0.4 Hz (HFa_{HP}). The powers of all spectral components falling within these bands were summed up. LFa_{QT} and HFa_{HP} were expressed in ms^2. LFa_{QT} is considered as an index of cardiac sympathetic modulation [9], while HFa_{HP} is an index of vagal modulation [10].

2.4. CRC Assessment

CRC was quantified using squared coherence (K^2) between HP variability and RESP series [11]. K^2 was

calculated as the square magnitude of the cross-spectral density between HP and RESP normalized by the product of their power spectral densities. K^2 ranged from 0 (no linear correlation) to 1 (perfect linear correlation). To estimate K^2, a parametric approach based on the bivariate autoregressive model was employed [8]. A fixed model order of 10 was utilized. K^2 was sampled at respiratory rate and this index was referred to as $K^2_{HP\text{-}RESP}$.

2.5. Statistical Analysis

One-way analysis of variance was applied to detect the differences between the three groups (*i.e.,* HFrEF, HFpEF, and CTRL). Kruskal-Wallis test was employed when appropriate. Post hoc comparisons were performed to account for the issue of multiple comparisons. Statistical analyses were performed using commercial software (Sigmaplot, Systat Software, Inc., Chicago, IL, version 11.0), with statistical significance set at $p<0.05$.

3. Results

Table 2 summarizes the time domain results in HFrEF, HFpEF and CTRL, respectively. No statistically significant difference was found across groups for the time domain indexes.

Figure 1 shows univariate and bivariate frequency domain markers across the different groups. HFa_{HP} (Fig.1a) and $K^2_{HP\text{-}RESP}$ (Fig.1c) were significantly lower in the HFpEF group compared to HFrEF one. $K^2_{HP\text{-}RESP}$ was significantly lower in HFpEF group than in CTRL subjects as well (Fig.1c). LFa_{QT} was significantly higher in the HFpEF group compared to the HFrEF (Fig.1b).

4. Discussion

The main findings of the present study can be summarized as follows: i) HFpEF exhibited an increased cardiac sympathetic modulation, and a reduced respiratory sinus arrhythmia compared to HFrEF; ii) these changes in autonomic regulation were mirrored by a lower CRC in HFpEF group with respect to HFrEF patients.

These findings suggest that adjustments of the autonomic modulation in HFpEF are necessary to maintain EF at normal levels and these modifications are still sustained by the heart and autonomic control. The elevated QT variability observed in HFpEF might be associated with very important changes of the sympathetic activity about the mean tonic level in response to the need to increase ventricular contractility to cope with the demand of the entire organism in the presence of a less efficient heart. This situation, in association with a lower vagal modulation, as indicated by a lower HFa_{HP} in HFpEF compared to HFrEF, delineates a condition of greater ventricular repolarization instability potentially increasing the risk for ventricular tachyarrhythmias, even in the presence of preserved systolic function [12]. Indexes assessing temporal instability of ventricular repolarization such as the amount of QT changes unrelated to HP variations [13] and periodic repolarization dynamics [14] might provide additional insight. We suggest that, while these compensatory mechanisms may increase arrhythmic risk, they could also be key in sustaining EF and preventing further deterioration of cardiac function, with possible impact on patient's functional capacity and symptoms. This altered autonomic pattern in HFpEF patients may reflect distinct pathophysiological mechanisms underlying this CHF phenotype, reinforcing the complementary value of mechanical indexes, such as EF, and indexes of the autonomic control.

Table 2. Time domain indexes in CHF patients.

Variable	HFrEF (n=9)	HFpEF (n=10)	CTRL (n=10)
μ_{HP} [ms]	850 ± 107	777 ± 113	746 ± 116
σ^2_{HP} [ms^2]	866 ± 637	1359 ± 966	1029 ± 353
μ_{QT} [ms]	367 ± 42	341 ± 53	323 ± 28
σ^2_{QT} [ms^2]	333 ± 324	301 ± 271	334 ± 246

CHF=chronic heart failure; EF=left ventricular ejection fraction; HFpEF=CHF with preserved EF; HFrEF=CHF with reduced EF; CTRL=control group; HP=heart period; μ_{HP}= HP mean; σ^2_{HP}= HP variance; QT= time interval between Q-wave onset and T-wave end (QT); μ_{QT}= QT mean; σ^2_{QT}= QT variance.

Simultaneously, CRC analysis has been shown to be a valuable and complementary tool to differentiate the CHF phenotype. As a matter of fact, the HFpEF group presented lower CRC strength compared to HFrEF and CTRL. While the physiological mechanisms remain under investigation, previous studies suggest that CRC can be an efficient method to demonstrate the neural interaction between heart and respiratory system [4]. In healthy conditions, an increased resting CRC strength may be linked to enhanced oxygen delivery and improved coordination of physiological subsystems to manage hypoxemic responses during intense physical activity [15]. Conversely, in individuals with cardiometabolic risk factors, reduced CRC has been identified as an early marker of autonomic dysfunction, even in the absence of alterations in traditional markers of HP variability. In the context of the present study, the observed reduction in CRC in HFpEF may reflect changes in autonomic modulation suggested by HFa_{HP} and LFa_{QT}. Indeed, it is well-known that sympathetic activation and vagal withdrawal reduced CRC [11]. However, the reduced CRC in HFpEF may indicate a potential adaptive response aimed at maintaining adequate cardiac output as well [5]. CRC might offer additional integrative insight by accounting from the dynamic interplay between heart and respiratory system, rather than

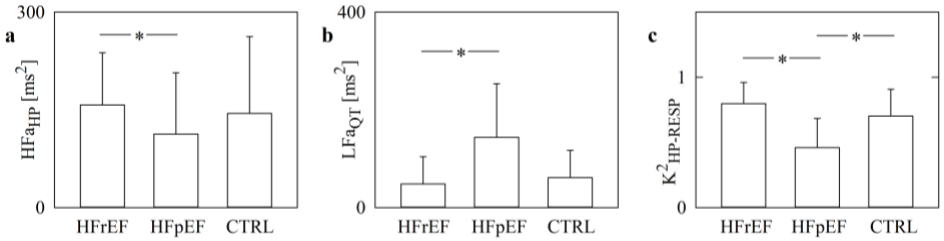

Figure 1. The vertical bar graphs show HFa_{HP} (a), LFa_{QT} (b), and $K^2_{HP\text{-}RESP}$ (c) across the three groups. The values are reported as mean plus standard deviation. The symbol * indicates a $p<0.05$.

assessing cardiac control in isolation. This broader perspective may reveal changes at the level of central respiratory network and its interactions with sympathetic drive and vagal modulation, particularly relevant in HFpEF patients. Furthermore, characterizing CRC may not only contribute to distinguishing between CHF phenotypes, but also support the development of targeted therapeutic strategies, potentially restoring autonomic balance and improving CRC in this population.

5. Conclusion

The strength of CRC is influenced by the phenotype of patients with CHF. A reduction in CRC was observed in patients with HFpEF, potentially indicating compensatory mechanisms aimed at maintaining proper cardiac function. These compensatory mechanisms might be driven by the possibility of increasing sympathetic modulation and decreasing vagal control. Although the underlying mechanisms remain not fully elucidated, we propose that the combined use of autonomic markers and a CRC index could be used for screening differences in CHF phenotypes for a deeper stratification of CHF population. The relevance of nonlinear dynamics in the assessment of CRC needs to be investigated as well [15].

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