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Original Article

Quantitative Assessment of Chronotropic Incompetence Using Time Domain Heart Rate Variability Derived from 24 – Hours Ambulatory Holter Monitoring

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ABSTRACT

Background : Chronotropic incompetence (CI) is defined as the failure of the heart to increase its heart rate along with activity and is an independent predictor of cardiovascular morbidity and mortality. The gold standard for CI is based on a treadmill test. However, up to now, there is no guideline to recommend whether CI could be concluded according to holter monitoring data.

Objective : This study aimed to determine CI based on Holter monitoring, specifically using time-domain analysis of heart rate variability (HRV).

Methods : This study used descriptive-analytic research with cross-sectional sampling. The population was patients that underwent treadmill and holter monitoring. The treadmill test was used as a gold standard of CI, and compare to holter monitoring using heart rate variability as a parameter. Data analysis used a comparative study (Independent T, Mann-Whitney, Chi-Square) and multivariate analysis logistic regression with a significance of $p < 0,05$.

Results: The subjects of the study were 111 patients with male-dominant (59 men). Standard Deviation N-N interval (SDNN) and Standard Deviation of Average N-N Interval (SDANN) were found lower in the CI group compared to the normal one. Mean SDNN was 113,57 + 51,08 msec in CI group and 117,4 + 39,48 msec in normal group with $p = 0.282$. Mean SDANN was 94,77 (73,42-118,85) in CI and 104,16 (74,9–139) with $p = 0.422$. While the Proportion of RR interval with the difference > 50 ms (RR50) and Average of All N-N Intervals (AVNN) found to be higher in CI group, but not statistically significant ($p = 0.681$; $p = 0.061$ respectively). Other parameter extracted from holter result, delta HR showed significant correlation with CI (50.5 (43,25-61,5) vs. 56 (50-72) with $p = 0.014$).

Conclusion: Time-domain HRV didn't had a significant correlation with CI. However, delta HR from holter monitor could be used as a predictor of CI.

1. Introduction

Chronotropic Incompetence (CI) is often stated as the inability of the heart rate to increase in order to accommodate increasing cardiac demand.[1] More specifically, CI described as the inability to achieve 85% of maximum predicted heart rate adjusted to age, according to astrand formula.[2] Physiologically, the heart rate will increase when the body system told it to do so.[3] A clear correlation between CI and increased mortality had been studied and established for decades.[1] Not only in patients with cardiovascular morbidity but also in those without any cardiovascular abnormality. Inability to reach 85% of age-adjusted - predicted maximum heart rate is a predictor of mortality and future cardiovascular events, even after adjusting age and other cardiovascular risk factors (HR 1.75 %; CI 95%).[4]

The ability to reach the age-predicted maximal heart rate (APMHR) using a treadmill test is the gold standard diagnostic tool for CI. But it was traditionally formulated in healthy people. However, there was no standardized measurement in cardiac disease. In heart failure patients, the standard diagnostic formula is proven not accurate. Therefore, the modified formula has been proven superiorly accurate in heart failure patients who tacking beta-blocker although there was still

some limitation.[5] Currently, many diagnostic approaches had been already proposed to make the diagnosis in certain cardiovascular conditions. But none of them showed a promising result.[6]

Holter monitoring had been widely used for diagnosing arrhythmia in clinical practice. Continuous monitoring of the patient can reflect the dynamic condition of the heart rate. Holter monitoring for diagnosing CI had been studied by lie et all in 2016. It showed that APMHR derived from a patient's daily activity could be used to diagnose CI.[7] HRV is widely used to measure autonomic function. HRV is one parameter that could be extracted from holter result. In our clinical practice, we used to make non – objective or eyeballing evaluation of patient heart rate fluctuation during 24 hours to determine the chronotropic competency. In this study, we tried to analyze holter monitor results and made a quantitative measurement of chronotropic competence using holter monitor parameters, specifically HRV parameter.

2. Methods

2.1. Study Design

This was a single-center observational analytic study, with a cross-sectional design. The study took place in Saiful Anwar General Hospital, Cardiovascular Integrative Unit (Instalasi Pelayanan Jantung Terpadu / IPJT). The study was approved by Saiful Anwar General Hospital and Faculty of Medicine Universitas Brawijaya's ethical committee. Written informed consent was derived from all of the participants.

2.3. Study Participants

This study used purposive sampling for sample recruitment. We involved the patients that came to our cardiovascular rehabilitation unit who undergone a treadmill test procedure for various indications. They are asked for a willingness to did an additional 24 hours Holter examination. We exclude the patient with cardiac pacemaker and patient who had been previously diagnosed with the following condition: atrio-ventricular block; frequent premature ventricular contraction (PVC) and patient with atrial fibrillation (AF).

2.4. Data Collection and Measurements

A total of 117 patients was performing both treadmill test and Holter monitoring, but due to not meet the inclusion criteria, only 111 patients were complete by the end of the study.

All the patients underwent a treadmill test using whether bruce or modified bruce criteria. Chronotropic incompetence was defined as an inability to achieve 85 % age-predicted maximum heart rate (APMHR) or inability to achieve 0.6 of a chronotropic index in patients who take beta-blockers as a part of their medication. Chronotropic index (maximum HR during activity – resting HR) divided by (APMHR – resting HR) is a standardized measurement of increasing HR during exercise.[8]

Holter monitor was performed for 24 hours using 12 leads BTL cardio-point H 300. Standard holter measurements were recorded, such as maximum HR, minimum HR, delta HR, and any arrhythmia that being recorded. Additional time-domain HRV were automatically extracted from the data by the factory software. They are SDNN (Standard Deviation N-N interval), SDANN (Standard Deviation of Average N-N Interval), RMSDD (Root Mean Square of the Successive Differences), and pNN50 (Number of Successive Differences between N-N interval that greater than 50 ms).

2.5. Statistical Analysis

Data were analyzed using SPSS for windows version 16. The comparison of CI and HRV parameters performed using paired student T-test if the data showed normal distribution or using Mann Whitney test if the data showed abnormal distribution.
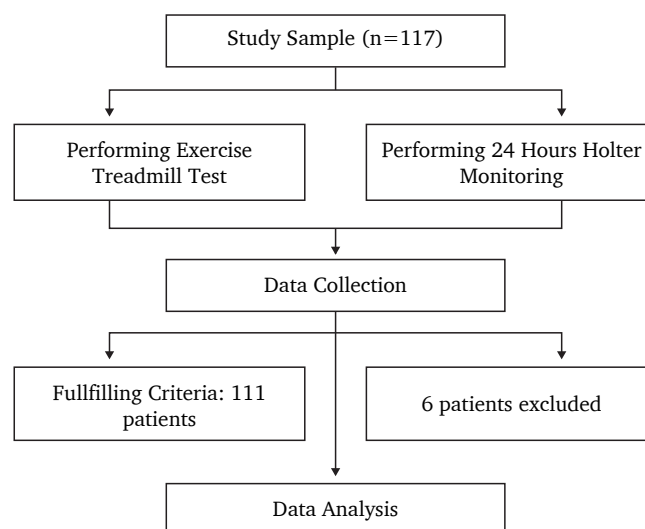

Figure 1. Study flowchart

3. Results

3.1. Baseline Characteristics

From July 2017 until January 2018, there were approximately 900 treadmill procedures was done in the Cardiac Rehabilitation Centre of IPJT Saiful Anwar General Hospital. 117 patients willing to perform an additional 24 hours holter monitor procedure and joining the study. Six patients were excluded because of arrhythmia found in the holter result. Most of them were atrial fibrillation (5 patients). CI was found in 52 patients (46.9 %). Of those in CI group 50 % (26 patients) were male. While in normal group 55.93% (33 patients) were male. Diabetes mellitus were found more frequently in CI group (21.15 % vs 6.78 %, p = 0.038). Coronary artery disease, heart failure, smoker and beta-blocker were higher in CI group, although not statistically significant (p = 0.49; p = 0,057; p = 0.45 and p = 0,13 respectively).

3.2. Time domain HRV

From HRV parameters extracted automatically from holter result. None of all the parameters were significantly correlated with CI. SDNN and SDANN were found lower in CI group compared to the normal group. Mean SDNN was 113,57 + 51,08 msec in CI group and 117,4 + 39,48 msec in normal group with p = 0.282). Mean SDANN was 94,77 (73,42-118,85) in CI and 104,16 (74,9–139) with p = 0.422. While the RR50 and AVNN found to be higher in CI group, but not statistically significant (p = 0.681; p = 0.061 respectively).

The only holter parameter that found to be promising was delta HR. The difference between the maximum and minimum HR in CI group was 50.5 (43,25-61,5) versus 56 (50-72) with p = 0.014.

3.3. Multivariate Analysis

At the beginning of the study, we planned to make a model to quantitatively calculate the possibility of CI from time-domain HRV

Table 1. Bivariate Analysis of Categoric Variables

Variables	CI Group (n=52)	Normal Group (n=59)	p
Male	26 (50%)	33 (55,93%)	
Diabetes Mellitus	11 (21,15%)	4 (6,78%)	0.038
Heart Failure	19 (36,54%)	12 (20,34%)	0.057
Smoker	23 (44,23%)	22 (37,29%)	0.45
Using beta-blocker	30 (57,69%)	17 (28,81%)	0.13
Coronary Artery Disease	23 (44.23%)	31 (52.5%)	0.49

Note, data were presented in mean ± SD or n(%)

Table 2. Bivariate Analysis of Numeric Variables

Variables	CI Group (n=52)	Normal Group (n=59)	p
Age	58,9 + 11, 46	55,7 + 11.2	0,138
SDNN (msec)	113,57 + 51,08	117, 4 + 39,48	0,282
SDANN (msec)	94,77 (73,42-118,85)	104,16 (74,9–139)	0,422
RR50 (msec)	5,51 (2,56-13,46)	4,95 (1,87-16,24)	0,681
AVNN (msec)	871,23 + 127,70	826,32 + 122,30	0,061
Delta HR (x/menit)	50,5 (43,25-61,5)	56 (50-72)	0,014

Note, data were presented in mean ± SD or n(%); SDNN, Standard Deviation N-N interval; SDANN, Standard Deviation of Average N-N Interval; RR50, Proportion of RR interval with the difference >50ms; AVNN, Average of All N-N Intervals ; HR, heart rate.

parameters, using logistic regression. The bivariate analysis p-value cut off was < 0.25. All parameters that had p-value < 0.25 will be eligible to join the next step analysis (logistic regression). Since there were only two holter parameters that had p-value < 0.25 (AVNN p = 0.061 and Delta HR p = 0.014), we decided not to continue to multivariate analysis.

4. Discussion

In this study, we found that only Delta HR is significantly correlated with CI (p 0.014). While other HRV parameters such as SDNN and SDANN were lower in CI group but not statistically significant. SDNN and SDANN reflect the sympathetic and parasympathetic activity. In patients with CI, HR failed to increase because of sympathetic activity was blunted. According to a previous study by Kawasaki et all, inability to reach APMHR in exercise (CI) is correlated with the ratio LF (Low Frequency) and HF (High Frequency), but not correlated with HF parameters.[20] Both HF and LF/HF ratios are the frequency domain HRV parameter. LF/HF ratio depicting sympathetic and parasympathetic, while HF is an index of parasympathetic tone.[21] AVNN and Pnn50 found to be higher in CI group compared to non-CI, although not reached statistically significant. Unlike SDNN and SDANN, AVNN and pnn50 are more specific for a higher parasympathetic tone.

Delta HR, which is a simple measurement extracted from holter results, also found to be a significant finding to predict CI. Patients with lower HR fluctuation found to be significantly correlated with the incidence of CI. Compared to eyeballing evaluation of HR fluctuation during 24 hours monitoring, delta HR offers more objective measurement. It opens the possibility for diagnosing CI using a currently popular and more simple wearable device, such as a smartwatch or smart band.

In this study, CI was found in 52 patients (46.8 %). According to ACC/AHA CI prevalence was ranged from 9 % to 89 %.[1] CI was found to be significantly higher in patients with diabetes mellitus type 2 (DMT2), heart failure, smoking, and bisoprolol therapy. Patients with DMT2 more likely to have CI, even after adjusting age, sex, and symptoms of CAD according to study among 12.291 patients.[9] Diabetic autonomic neuropathy that common in DMT2 patients has been believed to be responsible for the development of CI in DMT2 patients. Hyperglycaemia will cause oxidative stress and inflammation through activation of several metabolic pathways, such as Protein kinase C (PKC), hexosamine, and increase of Advance glycation end products (AGE).[10] It will end in systemic neuropathy, including autonomic neuropathy.[11]

CI is a predictor of the increment of all-cause mortality in patients with DMT2. Patients with CI and DMT2 developed a higher risk (hazard ratio 2.3; with 95 % CI 1.8 -3.1) compare to those with DM only or CI only (hazard ratio 1.7).[9]

Prevalence of CI also higher in heart failure patients according to our study. This result also matched with another previous study. The prevalence was ranged between 25 -70 % in various studies.[12] Patients with heart failure are at a higher risk of developing CI, despite any concomitant beta-blocking agent therapy or not.[13] The change in autonomic regulation, less contractility reserve, impaired physical activity, and beta-blocking agents contribute to the development of CI in HF patients.[14]

Data regarding the outcome of heart failure's patient with CI is not consistent. According to Yahya's study in 2010, CI was not a significant predictor of the worst outcome.[15] While another study indicated that the inability to achieve APMHR was an independent predictor of mortality in heart failure.[12,13,16]

Diagnosing CI in patients who take beta-blocker was a little bit different from those who don't. CI is common in patients with beta-blocker therapy.[17] The result from a cohort study in 3.736 patients who take beta-blockers as routine medication, the presence of CI was an independent predictor of death the worst outcome.[18] That's result came after adjusting age, gender, concomitant risk factor, and baseline heart rate. Discontinuation of the therapy didn't have a significant impact on reversing the CI in heart failure.[19] In contrast, the weight loss program and exercise cardiac rehabilitation would improve CI in CAD patients who take beta-blockers.17

Study Limitation

We only used one out of three HRV measurements in this study. According to the 1996 Task Force of European Society of Cardiology (ESC) and the North American Society of Pacing and Electrophysiology (NAPSE), HRV can be measured using three methods, time-domain, frequency-domain, and geometric method(22). Only time-domain HRV was involved in the measurement. Further study using a combination of time-domain, frequency-domain, and geometric analysis hopefully will have more power in predicting CI.

5. Conclusion

Time-domain HRV can't be used to predict CI according to the final result. However, Delta HR which is a simple measurement that depicting heart rate fluctuation during the day had a strong relation to CI.

6. Declarations

6.1. Ethics Approval and Consent to participate
This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involve in the study.

6.2. Consent for publication
Not applicable.

6.3. Availability of data and materials
Data used in our study were presented in the main text.

6.4. Competing interests
Not applicable.

6.5. Funding source
Not applicable.

6.6. Authors contributions
Idea/concept: AR. Design: AR. Control/supervision: MSR. Data collection/processing: AR, FSL. Extraction/Analysis/interpretation: AR, FSL. Literature review: MSR. Writing the article: AR. Critical review: MSR. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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