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Clinical Research

Evaluation of Cardiometabolic Factors Affecting Chronotropic Incompetence: A Cross–Sectional Retrospective Study in Sanglah General Hospital, Bali

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Abstract

Background: Recent studies have identified that chronotropic incompetence is correlated with poor cardiometabolic health and systemic inflammation that results in exercise intolerance, impaired quality of life and death due to cardiovascular disease (CVD). Unfortunately, there's still paucity of data regarding cardiometabolic factors associated with chronotropic incompetence. The purpose of this study was to identify the cardiometabolic factors associated with chronotropic incompetence.

Methods: This study was a cross-sectional retrospective study using cardiac treadmill stress test data at Sanglah General Hospital from May 2018 - May 2020 and 136 patients were enrolled. Data analysis used SPSS version 21. Pearson chi-square test was used to compare categorical variables based on cardiometabolic risk factors in chronotropic incompetence.

Results: Patients were divided based on the characteristics of age, gender, smoking status, body mass index, coronary artery disease, heart failure, hypertension, dyslipidemia, type 2 diabetes mellitus (T2DM), the levels of HbA1C, total cholesterol, LDL, HDL, and triglyceride. In this study, it was found that T2DM (PR 2.29; 95%CI 1.16–3.37), HbA1C (PR 3.13; 95%CI 2.31-4.22), dyslipidemia (PR 1.773; 95%CI 1.170–2.687), high total cholesterol (PR 2.396; 95%CI 1.650-3;481), and high LDL level (PR 1.853, 95%CI 1.229-2.794) were significantly associated with chronotropic incompetence (all p-value <0.05), while other factors were not significantly related.

Conclusion: Chronotropic incompetence can impair quality of life and contribute to cardiovascular mortality. However, T2DM, high HbA1C, dyslipidemia, high total cholesterol and LDL levels were found to be associated with chronotropic incompetence. This may contribute to higher cardiovascular risk attributed to those factors.

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Keywords: Chronotropic Incompetence, T2DM, HbA1C, Dyslipidemia, LDL, Total Cholesterol.

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Introduction

Exercise stress test (EST) is widely available and has been used for more than half a century for the evaluation of exercise related symptoms and assessment of cardiovascular diseases. Over the years, additional use and goals for exercise test have been evolved, including exercise prescription, evaluation of physical capacity and exercise tolerance, as well as assessment of arrhythmias, chronotropic competence, and therapeutic response to medications and implanted device interventions.[1] The ability to perform physical work is an important determinant of quality-of-life and is enabled by an increase in oxygen uptake (VO2).[1] During maximal aerobic exercise in healthy humans, VO2 increases approximately fourfold due to an increase in heart rate (HR) and stroke volume (SV) in response to exercise, although maximum HR will decrease with age.[2]

Chronotropic incompetence (CI) is generally defined as the inability to increase the HR adequately during exercise to match cardiac output to metabolic demands.[3,4] It is a measure of impaired cardiac performance, which is defined as the inability of the heart to increase its rate commensurate with increased activity or demand, such as during exercise.[4] Exercise CI itself is an established independent cardiovascular risk factor for major cardiac events and overall mortality, and might explain adaptation intolerance of the cardiovascular system to even minor exercise courses.[5]

Recent studies suggest that CI was associated with poor cardiometabolic health and the presence of systemic inflammation.[6,7] There are also studies showing that CI was associated with advanced age.[8] Several studies also shown that CI was correlated with a decrease in quality of life, and associated with mortality due to cardiovascular death. However, the data regarding risk factors for CI are still limited until now. Hence, this study aims to find out about the risk factors associated with CI.[9,10,11]

Methods

We conducted this cross-sectional retrospective study using cardiac treadmill stress test (TST) data at Sanglah General Hospital, Denpasar, Bali. Data were collected between May 2018 and May 2020. Data from 136 patients were enrolled in this study. The parameters that we evaluated in this study were baseline characteristics that is regarded as cardiometabolic risk factors (age, gender, body mass index/BMI, lipid profile, HbA1c levels, smoking status, type 2 diabetes mellitus, dyslipidemia, coronary artery disease, heart failure, rheumatoid heart disease and other cardiovascular disease) and Chronotropic Incompetence. Chronotropic Incompetence was defined as maximum heart rate that does not reach 85% of the predicted maximum heart rate based on age or Chronotropic Index that does not reach 80% during TST. Cut-off value for high HbA1c, high total cholesterol, high LDL, high triglyceride, and low HDL were 7.0%, 200 mg/dL, 100 mg/dL, 150 mg/dL and 40 mg/dL, respectively.

Data were expressed as mean ± standard deviation (SD) or number (percentage) and analysed using SPSS version 21. Numeric data were analysed using Mann-Whitney Test and categoric data were analysed using Pearson Chi-square Test to find an association between cardiometabolic risk factors and chronotropic incompetence.

Result

Baseline characteristics of patients shown in **Table 1**. Majority of patient were male (71.3%) with mean age was 48.7 years. Coronary artery disease was the most common previous cardiovascular disease, and the prevalence of CI in the study subjects was 37.5%.

Bivariate analysis between cardiometabolic risk factors and CI was shown in **Table 2**. In this study, there were no association between age, gender, BMI status, smoking status, and history of cardiovascular disease with CI (p-value > 0.05). In this study, it was found that high HbA1c level (PR 3.13; 95% CI 2.31 – 4.22), high Total Cholesterol level (PR 2.40, 95% CI 1.65 – 3.48), high LDL level (PR 1.85; 95% CI 1.23 – 2.80), Type 2 Diabetes Mellitus (PR 2.29; 95% CI 1.56 – 3.37) and dyslipidemia (PR 1.78; 95%CI 1.17 – 2.69) were significantly associated with CI with all p value <0.05.

Discussion

The exact mechanism of CI is still unclear, but in general CI defined as an abnormal response to an increase in pulse rate or chronotropic response during

Table 1. Baseline characteristics of patients.

Characteristics	[Mean ± SD]
Age (years)	48.7 ± 12.6
Gender	
Male [n (%)]	97 (71.3%)
Female [n (%)]	39 (28.7%)
BMI (kg/m2)	24.7 ± 9.2
Lipid Profile	
Total Cholesterol (mg/dL)	164.8 ± 42.2
LDL (mg/dL)	106.7 ± 34.5
HDL (mg/dL)	38.9 ± 13.4
Triglyceride (mg/dL)	144.9 ± 72.9
HbA1c	
High [n (%)]	16 (11.8%)
Normal [n (%)]	120 (88.2%)
Smoking Status	
Yes [n (%)]	9 (6.6%)
No [n (%)]	127 (93.4%)
CAD [n (%)]	82 (60.3%)
Heart Failure [n (%)]	51 (37.5%)
RHD [n (%)]	25 (18.4%)
Other cardiovascular disease [n (%)]	38 (27.9%)
Type 2 Diabetes Mellitus [n (%)]	28 (20.6%)
Dyslipidemia [n (%)]	32 (23.5%)
Hypertension [n (%)]	47 (34.6%)
Chronotropic Incompetence	
Yes [n (%)]	51 (37.5%)
No [n (%)]	85 (62.5%)

Table 2. Echocardiographic parameters of patients .

Parameters	[Mean ± SD]
EF	54.29 ± 13.76
EDV	85.71 ± 35.4
EDVI	46.2 ± 17.09
ESV	43.74 ± 25.13
ESVI	39 (28.7%)
FS	24.7 ± 9.2
IVSDd	9.95 ± 2.18
LVPWD	9.15 ± 2.17
LVIDd	45.26 ± 6.6
LVIDd I	25.57 ± 2.86
LVIDs	33.16 ± 6.72
LV Mass	125.17 ± 14.16
LV Mass Index	73.29 ± 19.96
TAPSE	18.45 ± 4.24
MV E/A	1.46 ± 0.76
MV D/T	178.29 ± 69.27
E/E'	13.01 ± 3.27
LAVI	31.66 ± 10.02
RHD [n (%)]	25 (18.4%)
Other cardiovascular disease [n (%)]	38 (27.9%)
Type 2 Diabetes Mellitus [n (%)]	28 (20.6%)
Dyslipidemia [n (%)]	32 (23.5%)
Hypertension [n (%)]	47 (34.6%)
Chronotropic Incompetence	
Yes [n (%)]	51 (37.5%)
No [n (%)]	85 (62.5%)

exercise in normal people which influenced by several components of the body's autoregulation, namely peripheral and central chemoreflexes, baroreflexes, mechanoreceptors and metaboreceptors in muscles, catecholamines, and electrolytes in plasma, as well as cardiac autonomic nervous regulation by the sympathetic and parasympathetic nervous systems.[12] In this study, cardiometabolic risk factors including T2DM, HbA1C, dyslipidemia, total cholesterol and LDL were associated with systemic inflammation, which were significantly associated with CI (all p-value <0.05), while the other variables were not significantly related.

Cholesterol and Chronotropic Incompetence

Our findings in this study are in line with the study conducted by Franssen et al. in 2021 which found that CI was significantly associated with total cholesterol levels and markers of systemic inflammation in the form of C-reactive protein with p-values respectively 0.012 and 0.039.[13] The possible mechanism was proposed by Lambert et al. that an increase in total cholesterol is accompanied by an increase in sympathetic activation, thereby inducing sympathovagal disbalance due to frequent sympathetic nerve activation. That will result in down-regulation of adrenergic receptors which can then lead to post-synaptic desensitization and thus interfere with sympathetically driven heart rate regulation during exercise.[14]

Although there were no studies that directly link LDL with the incidence of chronotropic incompetence, LDL along with total cholesterol levels were found

Table 3. Association between Cardiometabolic Risk Factors and Chronotropic Incompetence.

Cardiometabolic Risk	Chronotropic Incompetence		P-value PR (95%CI)
	Yes	No	
Age (years)	50.4 ± 12.5	47.7 ± 12.7	0.196
Gender			
Male	37 (38.1%)	60 (61.9%)	0.807
Female	14 (35.9%)	25 (64.1%)	1.06 (0.65 – 1.735)
BMI Status			
Obese	26 (51.0%)	25 (49.0%)	0.089
Overweight	8 (22.9%)	27 (77.1%)	
Normal	14 (34.1%)	27 (65.9%)	
Underweight	3 (33.3%)	6 (66.7%)	
Lipid Profile			
High Total Cholesterol	11 (78.6%)	3 (21.4%)	0.001*
			2.40 (1.65 – 3.48)
High LDL	19 (57.6%)	14 (42.4%)	0.006*
			1.85 (1.23 – 2.80)
Low HDL	18 (48.6%)	19 (51.4%)	0.101
			1.46 (0.95 – 2.25)
High Triglyceride	11 (52.4%)	10 (47.6%)	0.126
			1.51 (0.93 – 2.43)
HbA1c			
High	15 (93.8%)	1 (6.2%)	0.001*
Normal	36 (30.0%)	84 (70.0%)	3.13 (2.31 – 4.22)
Smoking Status			
Yes	4 (44.4%)	5 (55.6%)	0.728
No	47 (37.0%)	80 (63.0%)	1.20 (0.56 – 2.58)
Cardiovascular Disease			
CAD	36 (43.9%)	46 (56.1%)	0.057
			1.58 (0.96 – 2.59)
Hypertension	21 (44.7%)	26 (55.3%)	0.209
			1.33 (0.86 – 2.04)
Heart Failure	23 (45.1%)	28 (54.9%)	0.156
			1.37 (0.89 – 2.10)
RHD	7 (28.0%)	18 (72.0%)	0.277
			0.71 (0.36 – 1.38)
Others	15 (39.5%)	23 (60.5%)	0.767
			1.06 (0.67 – 1.72)
Comorbid Disease			
Type 2 Diabetes Mellitus	19 (67.9%)	9 (32.1%)	0.001*
			2.29 (1.56 – 3.37)
Dyslipidemia	18 (56.3%)	14 (43.8%)	0.012*
			1.78 (1.17 – 2.69)

*denotes statistical difference (p<0.05)

to have statistically significant association with Cardiac Autonomy Neuropathy (CAN) and decreased baroreceptor sensitivity due to atherosclerosis in the carotid arteries, with $p < 0.001$ for both.[15,16] The presence of CAN could interfere with autonomic nervous response and decreased baroreceptor sensitivity, which can lead in baroreflex disorders. This mechanism is thought to play a role in impaired chronotropic response to physical activity.[12]

Another proposed mechanism of dyslipidemia and CI, possibly due to suppression of catecholamine synthesis and release during physical activity due to excessive cortisol response. This condition is frequently found in obese individuals, where obesity usually occurs followed by dyslipidemia.[17] Previous studies have shown that epinephrine synthesis and release were significantly suppressed in obese adolescents during physical activity, which resulting in less stimulation of the SA node and consequently inhibition of the chronotropic response during exercise.[18,19] Low potassium levels are also commonly found in obese individuals, which also have the potential to cause CI,[20] but unfortunately, in our subjects neither catecholamine nor potassium levels were assessed.

Type 2 Diabetes Mellitus and Chronotropic Incompetence

Several previous studies stated that CI was commonly found in T2DM patients.[21,22,23] A study by Dominiq in 2014 showed similar results to our study, with the prevalence of CI was higher in patients with T2DM (42%) and a lower maximum chronotropic index than in patients without T2DM (with p-value<0.05).[23] Although there were still limited studies which directly link CI with HbA1c levels, the study by Dhumad et al.[24] Bhuyan et al.[25] Ahira et al.[26] showed high HbA1C level together with T2DM were significantly associated with cardiac autonomic neuropathy, whereas cardiac autonomic neuropathy was found to be more frequent and more severe in patients with longer duration of T2DM and poor glycaemic control, as represented by HbA1C values.

In the initial conditions, hyperglycaemia may result in increased sympathetic activity and resting HR, which in the long term will lead to the dominance of sympathetic nervous system activity. This long-term predominance of sympathetic nerves may lead to post-synaptic desensitization of b-adrenergic receptor pathways which downregulate of b-adrenergic receptors in sinoatrial node.[27-30] Since HR response to physical activity is determined by sympathetic influences to the heart and the ability of b-adrenergic receptors in the sinoatrial node to respond to circulating catecholamines, such desensitization may then result in impaired HR regulation and response during exercise.[31]

Chronotropic incompetence and aspects of life

Various studies have consistently shown that CI is associated with mortality and poor quality of life. The study by Muhammad et al. showed that there was a significant association of CI with cardiovascular mortality in population with normal ECG findings despite beta-blocker treatment. Kiviniemi et al and Gonzales et al also found similar results that chronotropic incompetence became a strong predictor of cardiovascular death in a population with comorbidities of acute coronary syndromes and chronic obstructive pulmonary disease.[32, 33, 34]

Although there have been no studies on the medical treatment of chronotropic incompetence or the results of controlling risk factors for the improvement of chronotropic incompetence, the results of a randomized control trial of cardiac rehabilitation in patients with chronotropic incompetence show that there is an increase in VO2 peak, improvement in chronotropic response, improvement in quality of life, and cardiovascular prognosis in subjects who underwent cardiac rehabilitation.[35,36]

Conclusion

Chronotropic incompetence may impair quality of life and causing cardiovascular mortality. However, T2DM, high HbA1C, dyslipidemia, high total cholesterol and LDL levels were associated with chronotropic incompetence. This may contribute to higher cardiovascular risk attributed to those factors.

Ethical Clearance

Ethical Clearance for this study was approved by Research Ethics Board of Faculty of Medicine Universitas Udayana decision letter number 1126/UN14.2.2.VII.14/LT/2021

Publication Approval

All authors read and approved final version of manuscript

Conflict of Interest

None

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