Increasing Age, Diabetes Mellitus and Beta Blocker Influence Heart Rate Recovery Values in Patients Undergoing Exercise Treadmill Test

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ABSTRACT

Background: Heart disease is the number one cause of death globally. This disease is initiation affected by autonomic dysfunction which will cause disruption of the sympathetic-parasympathetic system. Heart Rate Recovery (HRR) is used to determine autonomic dysfunction.
Objective: To determine the relationship of risk factors and cardiovascular treatment to HRR values of 1 minute and 2 minutes.
Methods: Cross sectional study to measure HRR 1 and 2 minute undergoing exercise treadmill test for the screening of coronary heart disease in Saiful Anwar hospital in May 2016 until September 2017. Univariate analysis was performed to determine the frequency and proportion of HRR values classified into normal groups (HRR 1 minute > 12x / minute or HRR 2 minutes > 22x / minute) and abnormal groups (HRR 2 minutes ≤ 12x / minute or HRR 2 minutes ≤ 22x / minute).We also performed bivariate analysis using comparative test (Generalized Linear Model) and correlation test (Pearson, Spearman and Eta) and multivariate linear regression analysis.
Results: This study found that age, hypertension and beta blocker were significantly associated with HRR abnormalities ($p<0.05$). HRR 1 and HRR 2 were significantly associated with diabetes mellitus (DM) ($p=0.004$ and $p=0.039$) and beta blocker ($p=0.042$ and $p=0.039$). Then looking at the relationship of multivariate correlations found a significant correlation between age ($\beta=-0.133$, $p=0.000$) and DM ($\beta=-2.617$, $p=0.032$) at 1 minute HRR and significant correlation with age ($\beta=-0.165$, $p=0.004$) and beta blockers ($\beta=-2,947$, $p=0.017$).
Conclusion : increasing of age, diabetes mellitus and beta blockers correlate with decreasing of HRR. The most influential risk factors for HRR values of 1 minute were increasing age and DM, while for HRR values of 2 minutes were increasing age and beta blockers.

Keywords: risk factor; treatment; heart rate recovery; exercise treadmill test

INTISARI

Latar Belakang: Penyakit jantung adalah penyebab kematian nomer satu secara global. Penyakit ini merupakan inti yang dipengaruhi oleh disfungsi otonom yang akan menyebabkan gangguan sistem simpatik parasimpatik. *Heart Rate Recovery* (HRR) digunakan untuk menentukan disfungsi otonom.
Tujuan: Untuk menentukan hubungan faktor risiko dan perawatan kardiovaskular dengan nilai HRR 1 menit dan 2 menit.
Metode: Studi *cross sectional* untuk mengukur HRR 1 dan 2 menit yang menjalani tes uji latih jantung tujuan skrining penyakit jantung koroner di rumah sakit Saiful Anwar pada Mei 2016 hingga September 2017. Analisis univariat dilakukan untuk menentukan frekuensi dan proporsi nilai HRR yang diklasifikasikan ke dalam kelompok normal (HRR 1 menit > 12x/menit atau HRR 2 menit > 22x/menit) dan kelompok abnormal (HRR 2 menit ≤ 12x/menit atau HRR 2 menit ≤ 22x/menit). Kita melakukan analisis bivariat menggunakan uji komparatif (*Generalized Linear Model*) dan uji korelasi (*Pearson, Spearman dan Eta*) dan analisis regresi linier untuk analisis multivariat.
Hasil: Penelitian ini menemukan bahwa usia, hipertensi dan *beta blocker* secara bermakna dikaitkan dengan kelainan HRR (p<0,05). HRR1 dan HRR2 secara bermakna dikaitkan dengan Diabetes Mellitus (DM) (p=0,004 dan p=0,039) dan b*eta blocker* (p=0,042 dan p=0,039). Kemudian melihat hubungan korelasi multivariat menemukan korelasi yang signifikan antara usia (β=-0.133, p=0,000) dan DM (β=-2.617, p=0,032) pada 1 menit HRR dan korelasi yang signifikan dengan usia (β=-0,165, p=0,004) dan *beta blocker* (β=-2,947, p=0,017).
Kesimpulan: Peningkatan usia, diabetes mellitus dan *beta blocker* akan menurunkan nilai HRR. Faktor resiko yang signifikan berpengaruh untuk nilai HRR 1 menit adalah usia dan DM, sedangkan untuk nilai HRR 2 menit adalah usia dan *beta blocker*.

INTRODUCTION

Heart diseases are the number one cause of death globally. An estimated 17.7 million people die from heart disease in 2015. This figure represents 31% of all global deaths.[1] Autonomic dysfunction in patients with coronary artery disease (CAD) is associated not only with abnormal heart function and structure, but also dependent other cardiovascular risk factors.[2] The condition of autonomic dysfunction is caused by an increase in inflammation which contributes to the process of atherosclerosis.[3] Myocardial electrical and contractile activity strongly was influenced by the autonomic nervous system through the balance of sympathetic-parasympathetic nervous system.

Heart Rate Recovery (HRR) is a combination of sympathetic withdrawal and parasympathetic reactivation.[4] HRR after exercise is emerging as a new and important prognostic index.[5,6] And an earlier study showed that a blunted HRR, which is defined as a decrease in heart rate (HR) of less than 12 beats/min from peak exercise to 1 min into recovery and less than 22 beats/minute from peak exercise.[7]

Several studies explain the relationship between autonomic activity that can be measured through HRR and plasma levels of inflammatory markers.[8] The relationship between autonomic dysfunction and risk factors for cardiovascular disease. The facts above made us to find out the relationship between risk factors and treatment with HRR values in patients who underwent exercise treadmill test at Dr. Saiful Anwar General Hospital Malang, Indonesia.

METHODS

This research has been approved by Ethical Clearance no: 400/129/K.3/302/2018 of Dr. Saiful Anwar General Hospital (SAGH). Analytical

design using a cross sectional approach was conducted to retrospectively evaluate the relationship between risk factors and treatment with Heart Rate Recovery (HRR) values for patients who performed cardiac training at the Cardiac Prevention and Rehabilitation Division of the Integrated Heart Service Installation at Dr. Saiful Anwar in May 2016 until September 2017.

The sampling technique uses a consecutive sampling method, which is that all subjects who come and hospitalized and meet the criteria as research subjects are included as research subjects until the required number of subjects is fulfilled. The sample in this study amounted to 338 people.

The inclusion criteria for this study were all patients who performed cardiac training with CAD screening goals aged 18-65 years which were known and validated by cardiac specialist cardiac rehabilitation consultants at SAGH; Patients undergoing the procedure with the Bruce protocol; and patients undergoing cardiac training tests for the purpose of CAD screening. Exclusion criteria for this study were patients with contraindications to cardiac training and cardiac rehabilitation (angina, systolic BP > 200 mHg, diastolic BP > 110 mmHg, decompensated heart failure, Total AV Block (TAVB)); patients are not the goal of screening for CAD; patients who have known CAD both with heart records and with Diagnostic Coronary Angiography (DCA); patients with a history of Coronary Artery Bypass Graft (CABG) revascularization and percutaneous coronary intervention (PCI); patients with cardiac arrhythmias atrial fibrillation and pacemaker use; patients with impaired renal failure; patients who have known peripheral vascular disease; patients with known heart valve disease and congenital heart disease; and patients with chronotropic incompetence and inadequate stress tests.

Statistical analysis (SPSS 20) t-test and Mann Whitney test were carried out. While other variables use the chi-square test. To determine the relationship between risk factors and HRR values based on the presence or absence of risk factor variables, Generalized Linear Model (GLM) was tested because of two measurements, namely at 1 minute HRR and 2 minutes HRR. Age variables, using Pearson correlation, Body Mass Index (BMI) with Spearman correlation test while other variables use the eta correlation test. Multivariate analysis to determine the effect of risk factor variables on HRR values simultaneously.

RESULT

The characteristics of the factors that influence HRR values are presented in Table 1, including age, sex, BMI, hypertension, smoking, diabetes mellitus (DM), beta blocker, calcium channel blocker (CCB), and positive ischemic response.

Table 1 shows the mean age in the normal group 49 years HRR and 52 years in abnormal HRR. Male gender was more in the normal HRR group (64.7%). Female sex was more prevalent in the abnormal HRR group (46.1%). The most risk factors in the combined two groups were hypertension (40.2%), smoking (28.4%), DM (9.4%), and BMI with a mean value of 27 kg / m2. Hypertension (46.8%), DM (12.3%) and beta blocker (15.1%), as well as non-dihydropyrydine CCB (8%) more in the abnormal HRR group. Smoking (16.6%) and Dihidropyrydine CCB (1.8%) were more common in the normal HRR group. Exercise treadmil test results showed a greater positive ischemic response in normal HRR of (11.2%). Table 1 shows the variables of age, hypertension and beta blocker have a significant relationship with HRR abnormalities.

Table 2 shows that HRR values 1 and 2 are significantly associated with DM and beta blockers.Table 3 shows that age has a weak and negative relationship to HRR 1 and HRR 2, the older the patient will be reduced the HRR 1 and HRR 2.

Table 1. Characteristics and factors affect normal or abnormal HRR 1 minute and 2 minutes

Variable	Normal HRR (n = 184) (HRR 1 > 12x/mnt or HRR 2 > 22xmnt)	Abnormal HRR (n = 154) (HRR 1 ≤ 12x/mnt or HRR 2 ≤ 22xmnt)	P value
Age	49 (19-65)	52 (23-65)	**0.005***
Gender			
- men	119 (64.7%)	83 (53.9%)	0.057
- women	65 (35.3%)	71 (46.1%)	
BMI	27 (2.88-41)	27 (2.56-37.10)	0.987
Hypertension	64 (34.8%)	72 (46.8%)	**0.034***
Smoking	56 (16.6%)	40 (11.8%)	0.433
Diabetes Mellitus	13 (7.1%)	19 (12.3%)	0.144
Beta Blocker	40 (11.8%)	51 (15.1%)	**0.026***
Calcium Chanel Blocker			
- Non Dihydropiridine	6 (1.8%)	5 (1.5%)	1.000
- Dihydropiridine	20 (5.9%)	27 (8%)	0.108
Positive ischemic response	38 (11.2%)	36 (10.7%)	0.638
HRR 1 minute	18 (13-34)	10 (0-27)	-
HRR 2 minute	33 (23-68)	21 (4-52)	-

Data presented in numbers (%), except age and BMI in mean ± SD, HRR in median (min - max);
* Significant relationship, if p value <0.05

Gender has a weak positive relationship with HRR 1, man can increase HRR 1. DM, beta blocker, and Dihydropyrydine CCB have a weak positive relationship with HRR 1 and HRR 2, meaning these variables will increase HRR1 and HRR 2 value.

Table 4 shows the relationship between age and DM affecting HRR1. Linear regression results are obtained as follows: Estimated HRR = 21.592 – 0.133 age – 2.617 DM. The magnitude of the contribution of the two variables in predicting HRR1 is 5.4%

Table 5 shows age and beta blockers affecting HRR 2 minutes. From the linear regression results, the following models are obtained: Estimated HRR = 37.989 – 0.165 age– 2.947 beta blocker. The magnitude of the contribution of the two variables in predicting HRR2 is 4.2%.

DISCUSSION

An abnormal HRR values were higher at average age than normal HRR according to studies that reported a higher mean age of abnormal HRR caused by a gradual decrease in autonomic control of the pulse in the aging process.[9,10]

Male gender was higher in the normal HRR group, but in males the distribution of HRR abnormalities (53.9%) was more than HRR in females (46.1%). This shows the difference in the sample population. Other studies showed male gender at HRR abnormalities (74%) more

Table 2. Relationship between risk factors with HRR values of 1 minute and HRR of 2 minutes based on variables

Variable	N (%)	HRR 1 minutes (nilai p)	HRR 2 minutes (nilai p)
Gender			
- man	202(59.8%)	0.085	0.489
- women	136(40.2%)		
BMI			
- Underweight		0.833	0.706
- Normal		0.086	0.134
- Overweight		0.398	0.630
- Obesitas		0.260	0.379
Hypertension			
- yes	136(40.2%)	0.721	0.528
- no	202 (59.8%)		
Smoking			
- yes	96(28.4%)	0.144	0.676
- no	242 (71.6%)		
Diabetes Mellitus			
- yes	32 (9.5%)	**0.004***	**0.039***
- no	306 (90.5%)		
Beta Blocker			
- yes	91(26,9%)	**0.042***	**0.004***
- no	247(73,1%)		
Calcium Chanel Blocker			
- Non Dihydropyridine	11(3.3%)	0.900	0.871
- Dihydropyridine	47 (13.9%)		
Ischemic response			
- Positive	74(21.9%)	0.895	0.737
- Negative	265(78,1%)		

* Significant relationship if the value of $p < 0.05$, based on bivariate analysis with the Generalized Linear Model test

than women in abnormal HRR values (26%).[9]

More hypertension in the abnormal HRR group was in accordance with studies that reported hypertension was more common in the abnormal group.[11] More smoking in the normal HRR group. This result contrasts with studies reported more smoking in the abnormal HRR group.[9] This difference can be caused because it is not known when patients start smoking and stop smoking, and more new smokers or a history of smokers who have stopped long.

Diabetes Mellitus and beta blocker were more prevalent in the HRR abnormal group according the study which reported DM and beta blocker were more prevalent in the abnormal HRR group.[9] This is related to cardiovascular autonomic neuropathy affects peripheral autonomic nervous system in innervating the heart and blood vessels.[2]

Dihydropyridine CCB more common in the normal HRR group, whereas, non dihydropyrydine CCB more abnormal in the HRR group. Previous studies showed more proportions of non-dihydropyrydine CCB in the abnormal HRR group and patients using CCB could significantly reduce HRR compared to those not using CCB.[2,9] Nondihydropyridine CCB, and beta blockers can reduce HRR after exercise.[12]

Table 3. Correlation of Risk Factors Variables to HRR 1 and HRR 2

Variable	Correlation coefficient (r)	
	HRR1	HRR2
Age	-0.230[a]	-0.178[b]
Gender	0.094[c]	0.038
BMI	-0.066	-0.063
Hypertesion	0.019	0.034
Smoking	0.080	0.023
Diabetes Mellitus	0.155[c]	0.112[c]
beta blocker	0.111[c]	0.156[c]
Calcium Chanel Blocker		
- Non Dihydropyridine	0.007	0.009
- Dihydropyridine	0.097[c]	0.107[c]
Positive Ischemic response	0.007	0.018

[a] r > 0.09 = multivariate test can be done, based on the Spearman correlation test
[b] r > 0.09 = multivariate test is feasible, based on Pearson correlation test
[c] r > 0.09 = multivariate test is feasible, based on Eta correlation test

Table 4. Multivariate Linear Regression of HRR 1 minute

Variable	B	Sig.
Age	**-0.133**	**0.000***
Gender	-1.086	0.127
BMI	-0.379	0.310
Diabetes Mellitus	**-2.617**	**0.032***
beta blocker	-1.109	0.164
CCB Dihydropyridine	-0.757	0.467
Adj R^2		**5.4%**

* Significant relationship if the value of p <0.05

Table 5. Multivariate Linear Regression of HRR 2 minutes

Variable	B	Sig.
Age	**-0.165**	**0.004***
Gender	-1.086	0.127
BMI	-0.386	0.504
Diabetes Mellitus	-2.861	0.126
Beta Blocker	**-2.947**	**0.017***
CCB Dihydropyridine	-0.797	0.979
Adj R^2		**4.2%**

* Significant relationship if the value of p <0.05

Exercise treadmill test results showed a positive ischemic response in normal HRR greater than the abnormal group. This data different from previous studies where more positive ischemic responses were found in abnormal HRR.[13] This may occur if this positive ischemic response has not disturbed the HRR value.

Age, hypertension and beta blocker have a significant relationship with HRR abnormalities. This is consistent with studies that report an increase in age associated with a decrease in HRR and the presence of a hypertensive relationship with a decrease in HRR values.[14,15] Some studies still contradict the use of beta blocker data on HRR. Previous research has shown post-HRR exercise is not significantly affected by beta blockers.[11]

HRR 1 and HRR 2 values are related to DM and beta blocker. DM is an important and independent risk factor develops into autonomic neuropathy which will cause abnormalities in heart rate control (HR).[16,17]

The correlation of age to HRR1 and HRR2 is weak with a negative direction according to previous studies which mention aging with a decrease in autonomic nervous system activity, is positively correlated with age because parasympathetic decreases with age.[18]

Gender showed no significant correlation at HRR 1 and HRR 2. These results are different from previous studies, where there was a significant difference between HRR values at 1 minute and HRR 2 minutes.[19] Different of the results in previous studies because dependent of neurohormonal factors concentrations of epinephrine and high basal plasma norephinephrine after exercise.[19]

BMI shows a negative correlation. These results are consistent with previous studies that increasing BMI will give a significant difference in the decrease of HRR.[20] Hypertension, smoking, gender, DM, Beta blocker and CCB will increase the value of HRR. This result is different from previous studies where these risk factors reduce HRR but this can be due to the factors that influence each other. Age and DM affect HRR 1 minute. Aging increases cardiac autonomic dysfunction associated with the onset and worsening of heart disease.[21] DM decreases HRR 1 minute. This result is different from the results of the bivariate test, it can be caused by many other factors that influence it. Age and beta blockers affect HRR 2 minutes in a negative direction. HRR is an independent prognostic factor related to death due to cardiovascular disease and its decreased response has been observed in patients with beta blockers.[22,23]

Beta blockers were significant in HRR 2 minutes compared to HRR 1 minute because beta receptor desensitization contributed a decrease in HRR more during the first 2 minutes of recovery, both autonomous branches contributed to the final recovery.

The limitations of this study are retrospective studies with medical records that cannot control confounding and bias factors. Factors wich confound HRR values were heart failure, cardiac profiles that cannot be seen in all patients, different judgments due to differences in doctors or accompanying medical personnel. Other risk factors such as dyslipidemia, other treatments, and fitness status cannot be removed.

CONCLUSION

The conclusion of this study is increasing of age, DM and beta blockers correlate with decreasing HRR values. The most influential risk factors for HRR values of 1 minute were age and DM, while for HRR values of 2 minutes were age and beta blockers.

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