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Improvement in diagnostic accuracy of exercise test with st/hr hysteresis in detection of significant coronary artery disease

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ABSTRACT

Introduction: The epidemiological shift increases the burden that come from non-communicable disease such as coronary heart disease (CHD). Our current gold standard for diagnosing CHD remains the invasive angiography procedure. Alternative diagnostics such as cardiac exercise test with ST changes standard have limited diagnostic capacity. A newly studied alternative is the ST/HR hysteresis. This study aim to compare diagnostic capacity of cardiac exercise tests using different standards: ST change and ST/HR hysteresis.

Methods: This study employed case-control diagnostic study design. Samples were recruited consecutively from patients registered in cardiology polyclinic in Sanglah General Hospital during period of study. Exclusion criteria include asymptomatic stent placement, post-coronary bypass, and patients with incomplete data. Data were obtained from medical records and analyses performed included descriptive analyses, ROC analyses, and sensitivity-specificity analyses using IBM SPSS 25.0 software.

Results: Samples totaled 134 subjects, 106 of whom were male (79,1%) and 27 (20,9%) female. Mean age was 55,4 + 8,8 years old. Of 134 subjects, 59 were confirmed to have CHD based on angiography results meanwhile 75 subjects were not found to have significant coronary arterial lesion. ROC analyses put cut off point for ST/HR hysteresis at 0,026 mV and based on this cut off point 58 were grouped as CHD-suspect (> 0,026 mV) and 76 were not. Sensitivity and specificity was 79,7% and 85,3% respectively. Based on diagnostics cross-tabulation we calculate net reclassification improvement which stood at 0,28.

Conclusion: Cardiac exercise test using ST/HR hysteresis as diagnostic standard with cut-off point of 0,026 mV was found to be an improvement on diagnostic capacity compared to standard ST change standard. More studies need to be performed to account for the different results found in different population.

Keywords: Coronary heart disease, cardiac exercise test, ST change, ST/HR hysteresis
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ABSTRAK

Pendahuluan: Pergeseran epidemiologis meningkatkan beban yang berasal dari penyakit tidak menular seperti penyakit jantung koroner (PJK). Standar emas saat ini untuk mendiagnosis PJK tetap merupakan prosedur angiografi invasif. Diagnosis alternatif seperti uji latih jantung dengan standar perubahan segmen ST memiliki kapasitas diagnostik terbatas. Parameter alternatif adalah histeresis ST/HR. Penelitian ini bertujuan untuk membandingkan kapasitas diagnostik uji latih jantung menggunakan standar yang berbeda: perubahan ST dan histeresis ST / HR.

Metode: Penelitian ini menggunakan desain studi diagnostik kasus-kontrol. Sampel direkrut secara berurutan dari pasien yang terdaftar di poliklinik kardiologi di Rumah Sakit Umum Sanglah selama masa studi. Kriteria eksklusi meliputi pasien post-stent yang asimptomatik, pasca operasi pintas koroner, dan pasien dengan data yang tidak lengkap. Data diperoleh dari rekam medis dan analisis yang dilakukan termasuk analisis deskriptif, analisis kurva ROC, dan analisis spesifisitas sensitivitas menggunakan perangkat lunak IBM SPSS 25.0.

Hasil: Sampel berjumlah 134 subjek, 106 di antaranya adalah laki-laki (79,1%) dan 27 (20,9%) perempuan. Usia rata-rata adalah 55,4 + 8,8 tahun. Dari 134 subjek, 59 dikonfirmasi memiliki PJK berdasarkan hasil angiografi, sementara 75 subjek tidak ditemukan memiliki lesi arteri koroner yang signifikan. Analisis ROC menempatkan titik cut-off untuk histeresis ST / HR pada 0,026 mV dan berdasarkan pada titik cut-off ini 58 dikelompokkan sebagai PJK (> 0,026 mV) dan 76 tidak. Sensitivitas dan spesifisitas masing-masing adalah 79,7% dan 85,3%. Berdasarkan tabulasi silang diagnostik kami mendapatkan peningkatan reklasifikasi bersih yang berada di 0,28.

Kesimpulan: Uji latih jantung dengan menggunakan histeresis ST / HR sebagai standar diagnostik dengan cut-off point 0,026 mV ditemukan peningkatan kapasitas diagnostik dibandingkan dengan standar perubahan segmen ST. Penelitian lebih lanjut perlu dilakukan untuk menjelaskan hasil yang berbeda yang ditemukan pada populasi yang berbeda.

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INTRODUCTION

The present phase of epidemiological transition is mainly driven by the change in the cause composition of mortality and morbidity, with the disease burden shifting from infectious diseases and malnutrition to cardiovascular diseases.[1] Among those cardiovascular disease that is still the main cause of death in the world is coronary artery disease (CAD).[2] The prevalence of coronary artery disease in various countries is still high.[3] In 2015 it is estimated that heart disease is the main cause of death of 17.9 million people worldwide and is expected to increase to 23.6 million by 2030.[4] Meanwhile in Indonesia, the prevalence of heart disease in 2018 based on basic health research data is 1.5%, where the province of Bali has prevalence close to the national rate.[5] At our hospital (Sanglah General Hospital Denpasar) alone there were 10,974 patients with CAD who were enrolled in integrated cardiac services in 2016 (around 60.3% of total patients). Invasive coronary angiography remains the 'gold standard' in depicting epicardial CAD, although has a limitation in which it can only evaluate the coronary artery lumen, not the existing plaque. The diagnosis of CAD may classically also be supported by functional testing such as cardiac exercise test with electrocardiography (ECG) which has the advantage of being able to give important information about the causal relationship between ischemia and the occurrence of the patient's symptoms.[6]

Beside the paramount effect on mortality, cardiovascular disease either directly or indirectly becomes an economic burden, with an estimated cost of around USD 329.7 billion (around IDR 4,624 trillion, with an exchange rate of USD 1 = IDR 14,025).[4] While in Indonesia, based on the financial statements of the national health insurance in 2016, spent around IDR 4.2 trillion for chronic outpatient patients which include cardiovascular disease.[7] In this era of rising healthcare cost with an increase in the prevalence of cardiovascular disease a better allocation of funding (cost effective) for available resources is needed. Cardiac exercise test is a solution to the problem because it uses minimal costs, without radiation, also reliable and vital in the interpretation of diseases. Even in the initial conditions with normal electrocardiography, a reliable and relatively easy cardiac exercise test is performed with results comparable to Technitium-99 perfusion imaging.[8] However, in other studies it is stated that standard parameters using ST-segment depression during cardiac exercise tests have limited diagnostic capacity. The use of ST / HR hysteresis, which measures the continuous change of the ST-segment and considers the heart rate (HR) during exercise test, in several studies shows a higher diagnostic capability. ST / HR hysteresis is also better than the parameters derived from the cardiopulmonary exercise test (CPET).[9]

By knowing the limitation of the standard parameters used during cardiac exercise test to detect the presence of CAD, research will be conducted on the diagnostic capacity of ST / HR hysteresis in the cardiac exercise test for the detection of significant CAD. This research was conducted because the cardiac exercise test with minimal cost, without radiation, reliable, and easy to do still has great potential to be developed. By using ST / HR hysteresis we expect to increase the diagnostic capacity of the cardiac exercise test.

MATERIALS AND METHODS

We studied patients suspected of CAD who underwent both a standard cardiac exercise test and invasive coronary angiography from November 2016 until April 2019. To obtain ST / HR hysteresis value, the ST/HR diagram containing pairs of simultaneous ST segment depression and HR measurements was constructed with parameters assessed at baseline, at the end of each minute of exercise, at the stop of the exercise, and at the end of each of the first 3 consecutive minutes of post-exercise recovery. A continuous linear function was obtained by connecting the consecutive ST/HR data pairs of each single exercise and recovery phase. Then, the difference between the exercise and recovery curves was integrated over the HR from the minimum HR 3 min of recovery to the maximum HR (ΔHR-rec). The integral was divided by the HR difference over the integration interval in order to normalize the ST/HR hysteresis with respect to the recovery HR decrement, and therefore expressed in mV.[10] Practically, it already calculated automatically on cardiac exercise test system (GE Case Stress Test System, GE T2100 Treadmill). We performed a diagnostic study which use the obtained ST / HR hysteresis value, then we look for a cut-off based on a receiver operating characteristic (ROC) curve.

Samples were consecutively selected from all patients with suspected CAD who had undergone a cardiac exercise test and coronary angiography examination at Sanglah Hospital. We exclude patients with asymptomatic stented CAD, post-coronary bypass patients, and patients with incomplete data. The subjects studied are samples that have required data. Samples were taken from medical record and collected consecutively, i.e. sampling by assigning subjects who met the criteria as research samples until reaching the required number of samples.

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Data was obtained from medical records containing result of cardiac exercise test and coronary angiography, along with ST / HR hysteresis value conducted from December 2018 until April 2019. In the current study, we aimed to apply univariate analysis to describe the characteristics of the sample, and ROC analysis to find the optimal cut-off value to detect CAD. Meanwhile, the diagnostic analysis performed to obtain sensitivity, specificity, net reclassification improvement (NRI), and other diagnostic index. Data analysis was performed using the IBM Statistical Package for the Social Science (SPSS) Statistics 25 software. Our study was approved by local ethic committee and all procedures was completed with an informed consent.

RESULTS

Between November 2016 and May 2019, 997 consecutive patients were enrolled. After excluding non-eligible patients, 134 patients were finally included in this study. Among them, there are 106 male (79.1%) and 28 females (20.9%), with an average age of 55.4 ± 8.8 years (ranged from 33 years old to 74 years old). The study population was grouped into 2 groups based on the ST / HR hysteresis value from the cut-off (according to the results of the ROC curve analysis: 0.026 mV).

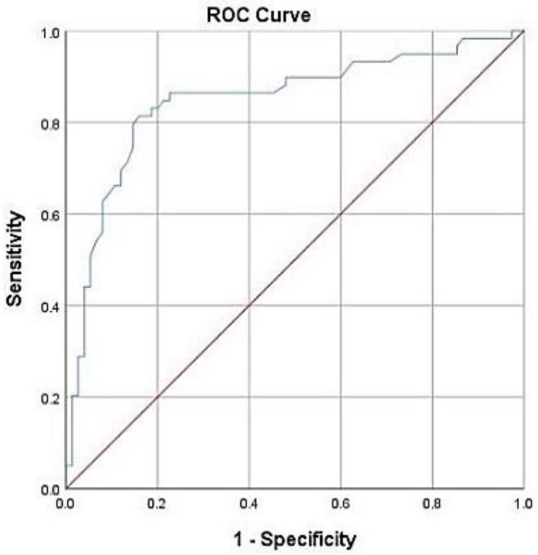

Figure 1 ROC curve in determining the cut-off value of ST / HR hysteresis to detect CAD

Table 1 Characteristics of the patients and research variables based on ST / HR hysteresis values (< 0.026 mV vs ≥ 0.026 mV)

Variable	ST/HR hysteresis	
	< 0,026 mV (n = 76)	≥ 0,026 mV (n = 58)
Age (mean ± SD)	54.14± 8.7	57.07±8.6
Sex, n (%)		
Male	59 (77.6%)	47 (81%)
Female	17 (22.4%)	11 (19%)
CAD, n (%)		
1-Vessel Disease	4 (5.3%)	14 (24.1%)
2-Vessel Disease	2 (2.6%)	17 (29.3%)
3-Vessel Disease	6 (7.9%)	16 (27.6%)
Left-main lesion	1 (1.3%)	9 (15.5%)
Normal angiography/ non-significant lesion	64 (84.2%)	11 (19%)
ST segment change, n (%)		
Positive	47 (61.8%)	54 (93.1%)
Negative	29 (38.2%)	4 (6.9%)

Table 2 Analysis of diagnostic capacity of ST / HR hysteresis

		Coronary Angiography (gold standard)	
		CAD (+)	CAD (-)
ST/HR hysteresis	CAD (+)	47	11
	CAD (-)	12	64

Sensitivity = 47:59 = 79.7%
Specificity = 64:75 = 85.3%
Positive predictive value = 47:58 = 81%
Negative predictive value = 64:76 = 84.2%
Positive likelihood ratio = 0.797:(1-0.853) = 5.42

A total of 58 patients had ST / HR hysteresis values ≥ 0.026 mV, while 76 patients with ST / HR values < 0.026 mV. Characteristics of the patients can be seen in table 1 above. Of total 58 patients who had ST / HR hysteresis values ≥ 0.026 mv, 47 patients (81%) have CAD. While from 76 patients with ST / HR hysteresis values < 0.026 mV, 64 patients (84.2%) were found with normal angiographic results or non-significant lesions. The use of ST / HR hysteresis value ≥ 0.026 mV to detect CAD has an area under curve (AUC) value of 84.8% (95% CI 77.7% -91.2%, p <0.001), 79.7% sensitivity and 85.3% specificity. The results of diagnostic analysis of ST / HR hysteresis compared to coronary angiography can be seen in table 2 below.

The results of the diagnostic analysis of ST / HR hysteresis are then combined with the analysis of ST-segment change criteria to detect CAD using net reclassification improvement (NRI) to find out whether there is an increase in accuracy of CAD diagnosis. In the calculation, the NRI is 0.28.

DISCUSSION

The subjects in this study amounted to 134 people consisting of 106 male (79.1%) and 28 females (20.9%), with an average age of 55.4 + 8.8 years

Table 3 Analysis of net reclassification improvement from the use of ST / HR hysteresis and the standard criteria using ST segment changes to detect CAD

CAD (+): upper left		Standard ST-segment change criteria				
CAD (-): lower right		Positif	Negatif	Total, split		Total
ST / HR hysteresis	Positive	45	2	47		58
		9	2	11		
	Negative	12	0	12		76
		35	29	64		
	Total, split	57	2	59		
		44	31	75		
	Total	101	33			134

NRI = (2 – 12): 59 + (35 – 2): 75 = 0.2764 ~ 0.28

(ranged from 33 years old to 74 years old). The findings of this study are consistent with other study results, where the proportion of male sex who suffered from CAD is more than female gender.[10] The age that is said to be at risk of developing CAD from a study that produced a predictive model of CAD is 55 years, while in another study it was said the risk of suffering from CAD began to increase after passing the age of 40 years.[11] The findings of those studies are consistent with the results of this study, where the average patient evaluated with suspected CAD was 55 years.

There were 59 patients with significant CAD (44%), meanwhile normal angiographic results / non-significant lesions were obtained in 75 patients (56%). The sensitivity and specificity value of ST-segment changes in this study were 64.4% and 49.3%, respectively. The result is comparable with statements in the cardiac exercise test guidelines, wherein the cardiac exercise test has limitations in diagnostic accuracy, sensitivity and specificity varying with a sensitivity range of 68% and specificity of 77%.[12]

In this study, a cut off point for ST / HR hysteresis for CAD detection of 0.026 mV showed good accuracy with an AUC of 84.8% (95% CI 77.7% - 91.2%, p <0.001), sensitivity 79.7% and specificity 85.3%. These results are similar to the results from previous study conducted by Bernabei with cut-off ST / HR hysteresis obtained also 0.026 mV, AUC 82% (95% CI 69.9-91.3, p = 0.001), and stated that the accuracy of diagnosis of ST / HR hysteresis was better than CPET.[13] In a study by Lehtiner, evaluating the use of ST / HR hysteresis in CAD detection even obtained an AUC value of 89% which was higher than the AUC value (76%, p<0.001) of using peak exercise ST-segment depression and ST-segment depression during recovery (84%, p = 0.006).[14] But in another study by Stanciu, who compared the results of perfusion imaging with an exercise test using dipyridamole, a different cut-off value of 0.015 mV was obtained.[15] This difference may be caused by differences in population and research methods used.

This study also evaluated the increase in diagnostic accuracy of the cardiac exercise test when we add the ST / HR hysteresis parameter using net reclassification improvement (NRI) analysis. NRI values are in the range of -2 to 2. In this study, the NRI result was 0.28, indicating that there was an increase in the ability to detect CAD by a cardiac exercise test when adding ST / HR hysteresis parameters.[16]

This study has several limitations, the selection of research subjects used consecutive sampling (non-random sampling) and the study was conducted using secondary data. In this study also has not thoroughly analyze the relationship of risk factors for ST / HR hysteresis. It also requires the development of research with long-term follow-up to determine the prognostic value of ST / HR hysteresis.

CONCLUSION

This diagnostic research has been carried out to highlight that ST / HR hysteresis has a better diagnostic accuracy than standard parameters have been used so far. Based on the results of the study, it concluded that ST / HR hysteresis ≥ 0.026 mV could potentially used as a parameter to detect the presence of coronary artery disease, and its use as a complement to the standard parameters of a cardiac exercise test accompanied by an increase in diagnostic accuracy.

The things that can be suggested based on the results of this study include the need for survival

research to assess the prognostic significance of ST / HR hysteresis. In addition, randomized research also needs to be done at multicenter using primary data.

DISCLOSURE

The authors report nothing to declare.

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