The association of rate pressure product (RPP) and myocardial perfusion imaging (MPI) findings: a preliminary study

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Abstract

Introduction: The product of heart rate and systolic blood pressure, termed as rate-pressure product (RPP), is a very reliable indicator of myocardial oxygen demand and is widely used clinically. There have been previous attempts to describe the relationship between RPP and the onset of pain in angina pectoris. The current study aimed to evaluate the association between RPP results and scan findings.

Materials and methods: In total, 497 patients with suspected coronary artery disease (CAD) underwent gated, single-photon emission computed tomography (SPECT) imaging with dipyridamole, exercise, or dobutamine stress, and were included in this study. Baseline and maximum heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and electrocardiogram (ECG) results were recorded. The rate-pressure product (RPP) was calculated as the product of heart rate and systolic arterial pressure for both baseline and maximum measures. The difference between the RPP max and the basal RPP is known as the RPP reserve. Researchers also obtained semi-quantitative analyses of myocardial perfusion imaging (MPI), using gated software, demographic information, risk factors of CAD, and pretest likelihoods of CAD using nomograms.

Result: Four hundred and ninety-seven cases, including 426 patients with dipyridamole stress, 59 with exercise stress, and 12 with dobutamine stress, underwent myocardial perfusion imaging. Scan results were positive in 194 (45.5%) and negative in 232 (54.5%) patients with dipyridamole stress. In patients with exercise stress, the scan was positive in 24 (40.7%) cases and negative in 35 (59.3%) cases. In dobutamine stressed patients, the scan was positive in 6 (50%) cases and negative in the 6 remaining cases. Dipyridamole stress resulted in a significant difference between HR at rest and at maximum (28.95 ± 24.53, p-value<0.0001), between systolic BP at rest and maximum (6.75 ± 12.50, p-value<0.0001) and between diastolic BP at rest and maximum (1.45 ± 5.80; p-value<0.0001). There was a significant correlation between sum stress scores (SSS) and reserved RPP (r= -0.12, p-value<0.001) which, in dipyridamole patients, was r=-0.18, p-value=0.0001). In addition, there was a significant association between reserved RPP and risk of CAD (p-value<0.001). In the patients with dipyridamole stress, the ejection fraction (EF) change (odds ratio =0.92; 95% CI: 0.86-0.98; p=0.01), reserve RPP (odds ratio =1.00; 95% CI: 1.00-1.00; p=0.04), risk of CAD (odds ratio =5.80; 95% CI: 3.21-10.50; p<0.0001) and age (odds ratio =0.94; 95% CI: 0.89-0.98; p=0.01) were associated significantly with MPI results, using multiple logistic regressions.

Conclusion. The study demonstrated that RPP is associated with MPI findings using gated SPECT imaging with dipyridamole stress. However, to confirm this preliminary result, further studies are mandatory.

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Introduction

Coronary artery disease (CAD) results from an imbalance between oxygen supply and the demands of the heart[1-3]. The need for oxygenated blood by the myocardium relates to heart rate, blood pressure, left ventricular contractility, and left ventricular wall stress[1,3-5]. Myocardial oxygen consumption (MVO_2) is a good indicator of the response of coronary circulation to increased myocardial oxygen demand[1,6,7]. The coronary blood flow (CBF) shows a linear correlation with the level of MVO_2[6,8,9]. Thus, the determinants of MVO_2 are also the determinants of CBF[1,6]. Direct measurement of MVO_2 is difficult in routine clinical practice, but it can be easily calculated by indirect methods using Stroke work, Pick's Principle, the tension time index, and rate pressure product (RPP)[1].

The product of heart rate and systolic blood pressure, termed as rate-pressure product (RPP), is a very reliable indicator of myocardial oxygen demand and it is widely used clinically, especially in anesthesiology and rehabilitation[10-12]. It is an easily measurable index, which correlates well with MVO_2 and defines the response of the coronary circulation to myocardial metabolic demands[13]. It is a good index of MVO_2 in patients with ischemic heart disease[13]. In patients with coronary artery disease (CAD), the occurrence of ischemic events has been shown to be related closely to increases in the rate-pressure product[14].

In addition, this important measurement is calculated in routine nuclear medicine practice during myocardial perfusion imaging; however, there are few reports specifically investigating RPP in nuclear medicine. This preliminary study was designed to evaluate the utility of RPP in the current practice of nuclear medicine.

Materials and methods

Participants. The study included 664 patients with known or suspected CAD referred for myocardial perfusion imaging using gated 99mTc-MIBI SPECT between November 2007 and June 2009. Each patient filled out a questionnaire that included demographics and risk factors for CAD. Of them, 173 patients had insufficient data, and 24 had an arrhythmia during MPI implementation; therefore, 497 patients enrolled in this study. The risk factors for CAD include: (1) hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or receiving antihypertensive drugs); (2) fasting blood sugar (FBS) ≥126 mg/dl or receiving hypoglycemic agents; (3) dyslipidemia (low density lipoprotein [LDL] >130 mg/dl or high density lipoprotein [HDL] <35 mg/dl or triglyceride [TG] ≥200 mg/dl); (4) smoking; (5) positive familial history (myocardial infarction [MI] or sudden death before the age of 55 for males and 65 for females among first relatives); (6) body mass index ≥30 kg/m². The pretest likelihood of CAD was estimated by means of nomograms that correlated the presence of diabetes with age, the ratio of cholesterol to HDL, gender, and smoking[15]. In addition, an abnormal ECG was designated as a 0.1 mV horizontal or down-sloping ST segment depression of 80 msec after the J point.

The research complied with the Declaration of Helsinki and the Institutional Ethics Committee of Bushehr University of Medical Science approved the study; all patients gave written informed consent.

Study protocol

Dipyridamole technetium-99m sestamibi SPECT protocol. Overall, 426 patients fasted overnight and all cardiovascular medications were discontinued at least two days before the study. An intravenous line of normal saline solution was connected to an antecubital vein, using a 20-gauge cannula. Dipyridamole (0.56 mg/kg) was infused over four minutes. Patients' symptoms and a twelve-lead ECG were monitored continuously. A dose of 740 MBq of 99mTc-sestamibi as a compact bolus was injected 4 minutes after the initiation of the infusion. Sixty minutes later, the patients ate a fatty meal to accelerate hepatobiliary clearance of 99mTc-sestamibi, and imaging followed 90 minutes after the initial infusion of dipyridamole. The rest phase was performed the next day.

Technetium 99m sestamibi SPECT exercise protocol. After the same precautions as described for the dipyridamole test, 59 patients exercised on a treadmill under a standard Bruce protocol. At the achieved peak heart rate (more than 85% of the age-predicted maximum heart rate), the appearance of typical angina, and/or positive exercise ECG findings, 740 MBq of 99mTc-MIBI was injected as a compact bolus. The exercise test was considered positive if there was a horizontal or down-sloping ST segment depression of more than 1 mm for 80 microseconds after the J point. An intravenous line of normal saline solution was positioned in an antecubital vein with a 20-gauge cannula. Imaging was performed 15–30 minutes after the exercise. On the next day, 60 minutes after an injection of 740 MBq 99mTc-MIBI, the patients ate a fatty meal to accelerate the hepatobiliary clearance of 99mTc-MIBI. The resting gated SPECT was performed 90 minutes after the 99mTc-MIBI injection.

Dobutamine technetium 99m-sestamibi SPECT protocol. In 12 patients, post IV infusion of sequentially increasing doses of dobutamine (starting at 10 μg/kg/min and reaching 40 μg/kg/min), 740 MBq of 99mTc-MIBI was injected intravenously, and a myocardial perfusion scan SPECT was performed in the stress phase as a dipyridamole test. The rest phase was tested on the following day.

Acquisition and processing protocols. A double-headed SPECT scintillation camera (ADAC Genesys, Malpitas CA,

USA) was used to acquire 32 views over 180º using a step-and-shoot method, progressing from 45º right anterior oblique to 45º left posterior oblique projections. A 20% symmetric energy window around the 140 keV Tc-99m photopeak and a low energy all-purpose (LEAP) collimator were applied, and the information was saved in 64 * 64 matrices. Acquisition time was 30 seconds per projection during rest and stress studies and 8 frames per cycle were applied. An expert nuclear medicine specialist used the cine display of the rotating planar projections to evaluate sub-diaphragmatic activities, attenuations, and patient motion to optimize the quality of the images. Processing was performed using a two-dimensional Butterworth pre-filter and a ramp filter for back projection to transaxial tomographic images. The transaxial views were realigned along the vertical long, horizontal, and short axes of the left ventricle. Acquisition parameters were identical for the rest and stress studies. For each patient, each of the three stress images was interpreted separately in comparison with the patient's rest image.

Visual and semi-quantitative SPECT analysis. For assessment, scans were divided into 20 segments, corresponding to the location of the territories of the various coronary arteries. A three-grade scale was used to evaluate the segments: normal perfusion, ischemic, and fixed segments. Ischemia was defined as the presence of a region with decreased or absent myocardial activity on exercise scans which improved on the rest stage images. A fixed segment was defined as a region of decreased or absent myocardial activity, both on exercise scans and on rest images.

In addition, gated short-axis images were processed using quantitative gated SPECT software (AutoQUANT; ADAC Laboratories, Maddison, WI, USA); the left ventricular ejection fraction (LVEF) and the summed stress score (SSS) were automatically calculated.

Rate pressure product (RPP) measurement

At first, the baseline HR, SBP, DBP, and ECG results were recorded and blood pressure was measured in the left arm of subjects by an aneroid sphygmomanometer. The ECG and HR were constantly displayed on a monitor and were recorded on paper at one-minute intervals. The patient's blood pressure was recorded every second minute for each stress type.

The rate-pressure product (RPP) was calculated as the product of heart rate (beats per minutes) and systolic arterial pressure (mmHg) multiplied by 10^{-3}.[4-6] The peak-rate pressure product was calculated by multiplying the maximum heart rate by the maximum systolic blood pressure attained for each stress type. It should be mentioned that peak HR in the dipyridamole group was defined as the highest HR during the observation period (before the administration of aminophylline, if that

happened), since the effects of dipyridamole could remain relevant after the completion of the infusion.

Basal RPP is the product of the resting HR and the resting systolic blood pressure. The difference between the RPP max and the basal RPP is known as the RPP reserve.

Statistical analysis

Continuous variables were expressed as the mean ± SD, and categorical variables as absolute values and percentages. Student's t-test compared the mean difference of the continuous variables between two groups; the comparison of categorized variables between the two groups was performed using the Chi-squared test. Researchers used the Statistical Package for the Social Science (SPSS) version 18 (SPSS Inc., Chicago, IL, USA) to perform the statistical analysis. A p-value <0.05 was considered statistically significant.

Results

The 497 test patients were comprised of 162 males (32.6%) and 335 females (67.4%). Four hundred and twenty-six patients underwent dipyridamole stress tests, 59 exercise treadmill tests (ETT), and 12 dobutamine stress tests. The mean age of patients undertaking dipyridamole tests was 58.80 ± 10.57 years (age range 22.00 - 97.00); for the exercise group, it was 51.32 ± 7.99 years (age range 38 - 72 years), and for those undertaking dobutamine tests, it was 54.00 ± 15.09 years (age range 25 - 72 years) (Table 1).

Dipyridamole patients had 34 positive ECG tests and 392 negative ECGs (426 cases); exercise produced 9 positive ECGs and 50 negative ECGs (59 case) and dobutamine patients had 3 positive ECGs and 9 negative ECGs (12 cases) (Table 1).

Scan results were positive in 194 (45.5%) patients and negative in 232 (54.5%) patients in the dipyridamole group. In the exercise group, the scan results were positive in 24 (40.7%) cases and negative in 35 (59.3%) cases. In the dobutamine group, the scan results were positive in 6 cases (50%) and negative in 6 cases (50%) (Table 1).

The maximum and reserve RPP values in the patients with normal and abnormal MPI showed a significant difference only in the dipyridamole group (p-value=0.04 and p-value=0.03). The ΔHR and the ΔSBP were also significant in the dipyridamole group between normal and abnormal MPI, while just the ΔHR was different in the exercise group (Table 2). In addition, neither was different in the dobutamine group, which may be due to the low number of cases in this subgroup (Table 2).

In the dipyridamole group, there was a significant difference between basal HR and maximum HR (ΔHR)

Table 1. Patient characteristics

Age		57.79±10.69 years
Male/Female		162/335
Smoking		60 (12.07 %)
IHD		84 (16.90%)
HLP		232(46.68%)
HTN		279(56.13%)
DM		150(30.18%)
FH		39(7.84%)
Risk of CAD	mild	282(56.74%)
	moderate	73(14.68%)
	high	81 (16.29%)
	very high	61(12.27%)
Chest pain	typical	234/497(47.08%)
	atypical	212(42.65%)
	non-specific	51(10.26%)

IHD, ischemic heart disease; HLP, hyperlipidemia; HTN, hypertension; DM, diabetes mellitus; FM, familial history; CAD, coronary artery disease.

(28.95 ± 24.53, p-value <0.0001), between basal and maximum systolic BP (ΔSBP) (6.75 ± 12.50, p-value <0.0001) and between basal and maximum diastolic BP (ΔDBP) (1.45 ± 5.80; p-value <0.0001); there was no significant difference between EF at rest and maximum (ΔEF) (-0.90 ± 9.82 %, p-value = 0.22) (Table 3).

In the exercise group, there was a significant difference between basal HR and maximum HR (ΔHR) (60.28 ±23.76, p-value <0.0001), between basal and maximum systolic BP (ΔSBP) (27.63 ± 83.44, p-value = 0.01),

between basal and maximum diastolic BP (ΔDBP) (4.35 ± 8.93; p-value <0.001), and between EF at rest and maximum (ΔEF) (-4.00 ± 7.63, p-value = 0.03) (Table 3).

In the dobutamine group, there was a significant difference between basal HR and maximum HR (ΔHR) (49.33 ±17.59, p-value <0.001), between basal and maximum systolic BP (ΔSBP) (16.25 ± 17.98, p-value = 0.01), and between EF at rest and maximum (ΔEF) (-7.57 ± 6.72, p-value = 0.02); there was no significant difference between basal and maximum diastolic BP (ΔDBP) (0.41 ± 6.55; p-value = 0.83) (Table 3).

There was a significant correlation between SSS and reserved RPP (r = -0.12, p-value <0.001) in all cases, but it was more pronounced in the dipyridamole group (r = -0.18, p-value <0.0001). In addition, there was a significant association between reserved RPP and risk of CAD (p-value <0.001) in all patients.

In the patients with dipyridamole stress, the EF change (odds ratio = 0.92; 95% CI: 0.86 - 0.98; p=0.01), reserve RPP (odds ratio =1.00; 95% CI: 1.00 -1.00; p=0.04), risk of CAD (odds ratio =5.80; 95% CI: 3.21-10.50; p<0.0001) and age (odds ratio = 0.94; 95% CI: 0.89 - 0.98; p=0.01) were associated significantly with MPI results, using multiple logistic regressions. However, the reserve RPP did not show such an association with MPI results in the same analysis of the exercise and dobutamine groups (p-value >0.05).

On the other hand, multivariate linear analyses, adjusting for main clinical risk factors, revealed that age, SSS, risk of CAD, and sex were the independent

Table 2. The rate pressure product values in the patients with normal and abnormal MPI in the three groups

Type of MPI	MPI result	Base RPP	P-value	Maximum RPP	P-value	Reserve RPP	P-value
Dipyridamole	Normal	10.92±3.15	0.50	16.10±5.11	0.04	5.25±4.21	0.00
	Abnormal	10.71±3.14		14.78±4.72		4.07±3.81	
Exercise	Normal	13.03±3.03	0.27	27.22±16.41	0.20	14.67±17.38	0.26
	Abnormal	12.17±2.56		22.66±6.93		10.49±6.01	
Dobutamine	Normal	10.91±2.88	0.40	19.95±5.89	0.40	9.03±5.38	0.70
	Abnormal	12.22±2.30		22.21±2.58		9.98±2.46	

MPI, myocardial perfusion imaging; RPP, rate-pressure product.

Table 3. The distinction of heart rate and blood pressure changes in the patients with normal and abnormal MPI in the three groups

Type of MPI	MPI result	ΔHR	P-value	Δsys. BP	P-value
Dipyridamole	Normal	30.97±24.98	0.06	7.92±14.23	0.01
	Abnormal	26.55±23.82		5.00±9.93	
Exercise	Normal	68.91±17.68	0.01	34.19±109.93	0.51
	Abnormal	53.95±25.41		19.16±21.24	
Dobutamine	Normal	56.00±22.37	0.54	10.00±12.64	0.24
	Abnormal	49.50±12.16		22.50±22.38	

MPI, myocardial perfusion imaging; HR, heart rate; sys.BP, systolic blood pressure; Δ, difference between rest and stress values.

Table 4. Multivariate linear analyses adjusting for main clinical risk factors for the prediction of reserve RPP across different models in the patients

Variable	RRPP		
	β	ρ	R2
Model 1			0.039
Age	–0.19	0.01	
Model 2			0.065
Age	–0.18	0.01	
SSS	–0.16	0.04	
Model 3			0.091
Age	–0.26	0.00	
SSS	–0.26	0.00	
Risk of CAD	–0.20	0.03	
Model 4			0.115
Age	–0.26	0.00	
SSS	–0.31	0.00	
Risk of CAD	–0.21	0.03	
Sex	0.16	0.04	

RRPP, reserve rate pressure product; SSS, sum stress score; CAD, coronary artery disease

determinants for prediction of reserve RPP across different models in the dipyridamole group of patients (Table 4).

Discussion

This study showed that RPP could be a predictor of myocardial ischemia in patients who underwent dipyridamole-stress MPI. The percentage increase in RPP using dipyridamole stress was significantly more in patients without CAD compared to patients with CAD, indicating better coronary perfusion in the former cases. On the other hand, the smaller percentage increase in the RPP of patients with CAD suggests significant compromise of coronary perfusion and decreased left ventricular function.

As mentioned, the hemodynamic response to dipyridamole is considered normal when it displays the effects of systemic vasodilatation, and HR increases as BP decreases[16,17]. The percentage increase in HR and SBP in dipyridamole stress was comparable in the two other study groups and the percentage increase in HR and SBP was significantly more in patients without CAD compared to patients with CAD.

The current study also showed associations among RPP reserve, SSS, and pretest likelihood of CAD in all patients and in the dipyridamole group. A decrease in the basal RPP and an improvement in RPP max results produced higher RPP reserves - the difference between these two values.

The increased RPP reserve means that the heart is capable of producing more work before showing any signs of ischemia; the heart is taxed to a lesser degree for the same intensity of exercise, making the perceived exertion lower for any given workload[13].

Previous investigations regarding exercise have revealed that RPP is valid as a predictive value of MVO_2 during exercise in patients with ischemic heart disease[18]. Other studies have shown that angina is precipitated by an increase in the work of the myocardium, as measured by RPP, to a critical value that is essentially fixed in each patient[19]. Subsequently, the peak RPP is an accurate reflection of the myocardial O_2 demand and workload. Reaching a high RPP without symptoms or evidence of severe ischemia suggests adequate left ventricular function. A low value of RPP reserve suggests significant limitation of coronary perfusion and decreased left ventricular function, which lead to angina.

HR and SBP are the most important variables determining changes in myocardial oxygen consumption between rest and exercise[19]. As reported earlier, there were significant increases in SBP, HR, and RPP with exercise, due to increases in sympathetic discharge[1]. HR, SBP, and RPP increase with increased workload on the heart to provide an adequate blood supply to the active myocardium during exercise. In the current study, RPP increased progressively with exercise and attained the peak value of 22.66 ± 6.93 mmHg × beats/min × 10⁻³ in patients with CAD and 27.22 ± 16.41 mmHg × beats/min × 10⁻³ in patients without CAD.

A previous study evaluated the association of RPP values with 37 individuals during exercise; 24 had ischemic heart disease (IHD) with a disease of 1, 2, or 3 vessels, and 13 had non-significant lesions of 1 vessel (less than 75%) or no coronary heart disease (CHD) on angiograms of the coronary arteries[18].

The researchers demonstrated that there was no distinction of RPP values between patients with CHD, with or without an ejection fraction less than 50%, or with or without disturbances of myocardial contractility, and normal individuals[18]. They mentioned that coronary vasoconstriction increased sympathetic tonus after exercise and that this resulted from increasing thromboxane A2 having a potent vasoconstrictive and platelet-aggregating effect, diminishing the anti-aggregatory effect of prostacyclin[18]. These researchers concluded that an excessive increase in the oxygen requirement of the myocardium was not the sole pathogenic mechanism of ischemia in patients with CAD[18].

In the current study, there was no significant difference in RPP values between patients with and without CAD in the dobutamine group.

In other studies, using positron emission tomography (PET), C-11–labeled palmitic acid has been used as a marker of oxidative metabolism[20,21]. The studies revealed that the clearance rate constant of [11C] acetate as an index of oxidative metabolism increased in relation to the increase in pressure-rate product during dobutamine

infusion in both left ventricular and right ventricular myocardium. They concluded that it could be used as a safe and valuable alternative for estimating the increase in oxidative metabolism in patients with various cardiac disorders[22]. In addition, Henes et al. showed an increase in Kmono in proportion to the increase in the pressure-rate product[23].

The significant difference in RPP, including max and reserve RPP, between patients with and without CAD only in the dipyridamole group remains unexplained. It is significant that RPP equals HR multiplied by BP and that BP is calculated by multiplying cardiac output (CO) by vascular resistance (VR)[24]. In addition, cardiac output (Q) equals stroke volume (SV) $\times$ HR[25]; therefore, RPP equals SV*VR*HR[2]. As a note to this equation, all three items are related to sympathetic nervous system activity and decreased parasympathetic nervous system activity. On the other hand, the principle in exercise and dobutamine stresses is based on sympathetic over-activity, which is observed in the patients with and without coronary disease (CAD), but dipyridamole stress is not affected by this issue. This hypothesis may illustrate the predictable role of RPP being limited to the dipyridamole MPI in the current study.

In total, the results may suggest that the measurement of RPP in response to physiological stress following dipyridamole during MPI implementation, and accompanied by other risk factors, signs, and symptoms, can help to detect CAD more accurately.

The current preliminary study had some shortcomings. The major limitation was the small sample size in the exercise and dobutamine stress MPI groups. The other limitation was the absence of coronary angiography as a gold standard test, since most of the patients were females and the sensitivity of diagnosing significant CAD utilizing MPI is low in females. Both of these limitations may have influenced the results of this study; therefore, these preliminary results should be validated in a larger, well-designed study.

Conclusion

The study demonstrated that RPP is associated with MPI findings using gated SPECT imaging with dipyridamole stress. However, to confirm this preliminary result, further studies are mandatory.

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