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Double Product as a Predictor of Coronary Artery Disease in Males with Normal Blood Pressure

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Abstract

Aim: This study investigates whether in males with normal blood pressure that underwent exercise stress test Double Product (DB) or Double Product Ratios to workload (DPR) are self-sufficient in predicting the presence of coronary artery disease (CAD). **Method:** 78 male patients with normal blood pressure went through bicycle exercise stress test (EST) and within four weeks they underwent coronary angiography. 34 of them resulted with normal coronary arteries and 44 of them were diagnosed with one or multiple vessel CAD. Pressure rate double product was calculated in rest, in the first stage of the exercise test, in the peak of exercise, and also in the second, fourth, and sixth minutes of recovery of the stress test. Also, the ratios of pressure rate double product with the workload, which reflects the relative growth of double product to the workload, were calculated. The results were compared between the two groups, the one with normal coronary arteries, and those with abnormal coronary angiography. **Results:** DP in rest and in the first stage of the exercise are not significantly different for normotensive males with or without CAD, while the peak DB value of the exercise, as well as the econd and sixth minutes of the recovery are significantly lower for the group of patients with CAD. The starting peak workloads were significantly lower in the patients' group with CAD ($p=0.0002$ and $p<0.0001$). On the other hand, the double product to workload ratio at the first stage was significantly lower in males with normal blood pressure and CAD. Significant lower DPR are detected also in the fourth and sixth minutes of recovery. **Conclusion:** The values of DP in the peak exercise and at the second and sixth minutes of the recovery phase are significantly lower in normotensive males with abnormal coronary angiography compared to those with normal coronary arteries, and these findings can be used to detect the presence of CAD despite the ECG changes and they are not affected by the baseline characteristics of the patients. The ratios between DP and workload at the first stage, and in the fourth and sixth minutes of recovery are significantly lower in normotensive male patients with coronary artery disease compared to those without CAD and can be independent predictive parameters for the disease.

Keywords: double product, double product ratios to workload, coronary artery disease, exercise stress test, normal blood pressure, male patients

Introduction

Pressure Rate Product (PRP), also known as the double product (DB), is used in exercise physiology to measure the stress put on the cardiac muscle based on the number of times the heart needs to beat per minute and the arterial blood pressure that pumps against. It is a good indicator of the energy consumption of the myocardial muscle.

DP = SBP x HR

The most important three determining factors of myocardial oxygen uptake are tension within the myocardium, its contractility, and heart rate. While exercising the values of the above three factors increase, the blood flow changes to balance oxygen supply with the increased demand. Double product closely reflects the directly measured myocardial oxygen uptake and coronary blood flow over a range of exercise intensity.

Standard values of DP vary from 6000 at rest (HR, 50b/min; SBP, 120 mmHg) to 40000 during very intense exercise (HR, 200 b/min; SBP, 200 mmHg) (Katch, McArdle, & Katch, 2010).

It is known that high levels of systolic blood pressure to workload rates in males with hypertension reveals the diagnosis of coronary artery disease despite the ECG variations during an exercise stress test, and this is not influenced by other basic characteristics of the patients (Temali & Kamberi, 2020). There are also researchers that have denied the prognostic importance of blood pressure response to exercise due to its rare reproducibility and lack of clinical finding characterizing those who consistently respond in this manner (Sharabi, et al., 2001).

It is also known that exercise heart rate is disproportionally increased with the increase of workload during exercise stress test in males with coronary artery disease (Kamberi, Heba, & Gjoka, 1999).

According to a study an increased systolic SBP and HR are predictors of death and disability in general population, but DB did not add to risk stratification over and beyond SBP and HR (Schutte, et al., 2013).

Systolic (SBP) and diastolic blood pressure (DBP) and mean arterial pressure (MAP) are risk factors for cardiovascular mortality (CVM). (Yazdani, et al., 2020) considered the DP as a marker of cardiac workload. They have examined the predictive value of DP to coronary angiography. DP proved to be an independent predictor of cardiovascular and all-cause mortality also in multivariate analysis.

However, Liu et al. (2019) found out that DB was significantly associated with all-cause and cardiovascular disease (CVD) mortality and the association between the DP and mortality would be stronger than that between mortality and SBP&HR, amplifying once more the importance of studying DP.

(Berman, Wynne, & Cohn) aimed to determine the value of a multivariate approach for the analysis of the treadmill exercise tolerance test (ETT). Predictive value of a positive ETT was 0.78 using 1.0-1.9 mm ST segment depression criterion. When the 1.0-1.9 mm ST criterion was combined with peak systolic blood pressure-heart rate product (double product) < 23,000, exercise duration less than 6 minutes, and ST depression for greater than 3 minutes into recovery, predictive value improved to 0.89. Predictive value for multivessel disease was also improved using non-ST criteria. Predictive value of a negative ETT for absence of coronary artery disease was 0.60, and was 0.86 if double product was > 30,000.

Rafie, et al. (2008) aimed to assess the prognostic power of double product (DP) parameters in patients referred for standard exercise testing. In this study population, DP reserve had greater prognostic power than metabolic equivalents, maximal HR or systolic blood pressure, or HR recovery.

Villella et al., (Am Heart J., 1999) researched the prognostic significance of DP to maximal symptom-limited exercise stress testing after myocardial infarction treated with thrombolytic agents. They showed that DP is a predictive index to assess prognosis in survivors of acute myocardial infarction treated with thrombolytic agents able to perform an exercise test after acute myocardial infarction, but its usefulness appears to be limited, considering that these patients were at low risk.

A study (Moradi & Fariba, 2017) compared the DP index before and after cardiac rehabilitation in patients undergoing coronary artery bypass grafting (CABG). The results of this study showed that the mean of the DP index, which is a quantitative criterion for the assessment of cardiac function, significantly increased after 12 rehabilitation sessions in patients who underwent CABG.

According to our view not only the peak blood pressure and peak heart rate determine the response of blood pressure and heart rate during recovery, but it is the workload that provokes the increase of heart rate and blood pressure during exercise, and thus during the recovery. Based on this, not only DB should be observed during exercise, but also the rate between DB and workload, known as DB index. Thus, in this study we investigated the relative response of pressure rate double product and its ratios to workload during exercise and recovery.

Methods

78 normotensive males aged 34-64 years old were involved in this study. All of them had gone through the progressive exercise stress test (EST) stage by stage with the goal of maximal physical effort according to the protocol of A. Kamberi (Kamberi A. , 1984). EST was performed with an ergonometric bicycle. All the patients underwent coronary angiography within four weeks. The patients were grouped according to the result of the EST and coronary angiography. Four of the patients were excluded from the study because of one of the four basic information.

Electrocardiogram (ECG) is registered at rest in sitting position, in the third minute of every stage of the exercise, and also in the second, fourth and sixth minutes of recovery. Blood pressure is measured in rest in laying position, sitting in the bicycle, and in the last 20 seconds of every exercise stage and in the second, fourth and sixth minutes of recovery.

The definition of hypertension is considered present when SBP is greater or equal to 140 mmHg, or when diastolic blood pressure is found equal to or greater than 90 mmHg (ESC Journal, 2019)

Pressure rate double product is calculated DP = Heart Rate (HR) x SBP / 100.

To show the relative increase during exercise and the relative decrease of pressure rate double product in the recovery, rates of DP are calculated as rDP = DP / Workload (W) respectively in rest, first stage, exercise peak, second, fourth, and six minutes of recovery.

The first stage DPR (DPRf) is calculated as the rate of the double product of the third minute of the exercise to the workload at that stage.

The peak DPR (DBRp) is the ratio of the peak DP to the peak workload.

The second, fourth and sixth DBR (DBR2, DBR4 and DBR6) are the ratios of DP to the peak workload.

The EST is considered as positive when during the exercise or the recovery it is found specific abnormal ECG.

As specific abnormal ECG is considered the presence of horizontal or down-sloping depression of ST segment equal or greater than 1 mm, 80 milliseconds away from the joint point S-ST, or when there is the elevation of ST-segment 1 mm or more starting from the J-point, or there is slow up-slopping depression of ST-segment. Also, the stress test is considered positive when there is angina provoked from exercise, in the absence of ECG changes.

The stress test is considered negative when it is achieved 85% or more of the target heart rate with no specific changes in EG or typical angina. In the absence of achievement of 85% of target heart rate, and of typical angina pectoris, the stress test is considered as non-conclusive.

All of the patients with normal blood pressure and EST are divided into two groups according to the coronary angiography result. Group I, 34 individuals with normal tension and normal coronary angiography, and Group II, 44 patients, with normal tension and abnormal coronary angiography. Each of them is analyzed according to the coronary angiography (Normal – Abnormal), and according to the EST.

Statistical Analysis

All the variables are compared between two groups with *t* test. The analysis of continuous variables is done with ANOVA for all groups and with Scheffe procedure with statistical level of significance of 5%. To determine the impact that other independent factors have to various values of DBR, stepwise regression method is used.

Results

Basic characteristics of normotensive males with normal or abnormal coronary angiography like age, weight, height, body mass index (BMI), ejection fraction, time of exercise, DP at rest and at the initial stage of the EST, the workload at the first stage and at the peak of the exercise, as well as the DP in the sixth minute after recovery, did not show statistical difference in both groups.

Meanwhile, the DP at the peak of exercise and in the second and sixth minute after recovery, in addition to the ratios of initial workload and peak workload to BMI were statistically higher in normotensive males with normal coronary arteries, respectively 298 versus 228 (p=0.001) for the peak, 163 versus 133 (p=0.0003) for the second minute of recovery, and 120 versus 108 (p=0.0390) for the sixth minute of recovery (Table 1).

Starting workload, peak workload and the percentage target heart rate achieved were significantly higher in normotensive males with normal coronary arteries as compared to normotensive males with coronary arteriopathy.

Table 1: Characteristic of normotensive males with normal and abnormal coronary artery disease

Characteristics	**Normal coronary Angiography Mean (SD)**	**P-Value**	**Abnormal coronary Angiography. Mean (SD)**
Age, years	44 (9.8)	**0.0004**	53 (9.7)
Weight, kg	75 (13)	0.4600	73.3 (8.4)
Height, m	1.70 (0.47)	0.6000	1.70 (0.5)
Body mass index	25.9 (4.03)	0.3200	25.2(2.5)
Ejection fraction, %	0.69 (0.09)	0.0600	0.64 (0.13)
DP at rest, mm Hg	91.8 (13.9)	0.4736	89.3 (16.6)
DP at the end of 1st exercise stage, mm Hg	143.6 (23.6)	0.3660	138 (29.5)
Peak DP, mm Hg	298 (60.2)	**<0.0001**	228.4 (63.3)

DP at recovery 2nd minute	162.5 (38.8)	**0.0003**	132.6 (29.3)
DP at recovery 4th minute	132.1 (29.6)	0.2310	117.8 (23.9)
DP at recovery 6th minute	119.9 (26.5)	**0.0391**	107.7 (23.4)
Starting work load, watt	39.4(10.1)	**0.0002**	31.4 (8.2)
Peak work load, watt	144.0 (38.2)	**<0.0001**	108.3 (35.7)
Exercise Duration, min	10.7 (3.0)	**0.0490**	9.2 (3.7)
Percentage target heart rate achieved	86.2 (11.2)	**<0.0001**	70.3 (11.4)

Table 2: Double Product Rates to workload in normotensive males with normal and abnormal coronary artery disease

Double Product Rates to workload	Normal coronary angiography	P-Value	Abnormal coronary angiography
	Mean (SD)		Mean (SD)
First stage DPR	3.921(1.288)	0.0247	4.655(1.484)
Peak DPR	2.137(0.457)	0.3478	2.278(0.708)
2nd recovery minute DPR	1.175(0.324)	0.0673	1.378(0.552)
4th recovery minute DPR	0.954(0.265)	0.0074	1.224(0.500)
6th recovery minute DPR	0.876(0.247)	0.0221	1.113(0.523)

Table 3: Mean Differences and Confidence Interval of Double Product Rates to workload in normotensive males with normal and abnormal coronary artery disease

TAN	**Mean Diff**	**Confidence interval**	
		95% lower	**95% upper**
First stage DPR	-0.734	-1.371	0.096
Peak DPR	-0.142	-0.440	0.157
2nd recovery minute DPR	-0.134	-0.265	-0.002
4th recovery minute DPR	-0.270	-0.468	-0.075
6th recovery minute DPR	-0.236	-0.438	-0.035

Regarding the rates of DB to the workload the first stage, the fourth and sixth minutes of recovery are statistically significant in normotensive males with coronary artery disease compared to normotensive males with normal coronary arteries (

Table 2).

So, the mean difference of the first stage of DPR is -0.734, confidence interval (CI) 95% from -1.371 till 0.096 (p=0.0247). In the fourth recovery minute the mean difference is -0.270, whereas the CI 95% ranges from -0.468 to -0.075 (p=0.0074), and in the sixth recovery minute the mean difference is -0.236, whereas the CI 95% ranges from -0.438 to -0.035 (p=0.0221) according to the analysis shown in

Table 2 and Table 3.

Stepwise regression analysis pointed out the determinant factors of every DPR specifically. It is very important to underline that BMI, weight, height, initial systolic blood pressure (SBPi), and diastolic blood pressure (DBPi) do not have any influence. On the other hand, the peak workload (Wp), the peak SBP (SBPp), the peak heart rate (HRp) are the most common independent determiners in various phases of the exercise stress test, regarding the double product rate. The respective results are displayed in Table 4.

Table 4: Mean Differences and Confidence Interval of Double Product Rates to workload in normotensive males with normal and abnormal coronary artery disease

SBP / Woarkload Rates Stages	Normal coronary angiography		Abnormal coronary angiography	
	Coefficient (MSE)*	Adjusted R^2	Coefficient (MSE)*	Adjusted R^2
First stage DPR				
Intercept	-0.369(0.500)	0.980	-0.512(0.721)	0.902
HRi (b/min)	0.039(0.003)		0.045(0.005)	
SBPi (mmHg)	0.028(0.002)		0.005(0.004)	
Wi (Watt)	-0.092(0.004)		-0.129(0.009)	
Peak DPR				
Intercept	1.078(0.320)	0.973	0.209(0.296)	0.897
DBPp (mmHg)	-0.012(0.004)			
HRp (b/min)	0.011(0.001)		0.021(0.003)	
SBPp (mmHg)	0.011(0.001)		0.010(0.001)	
Wp (Watt)	-0.013(0.0005)		-0.022(0.001)	
2nd recovery minute DPR				
Intercept	1.446(0.655)	0.814	1.310(0.361)	0.682
DBPp (mmHg)	-0.017(0.008)			
HRp (b/min)	0.005(0.001)		0.014(0.004)	
SBPp (mmHg)	0.008(0.001)			
Wp (Watt)	-0.008(0.001)		-0.017(0.002)	
4th recovery minute DPR				

Intercept	1.111(0.502)	0.839	0.611(0.404)	0.740
Age (years)	0.006(0.002)			
DBPp (mmHg)	-0.013(0.006)			
HRp (b/min)	0.005(0.001)		0.019(0.003)	
HRi (b/min)			0.011(0.005)	
SBPp (mmHg)	0.004(0.001)			
Wp (Watt)	-0.007(0.001)		-0.014(0.002)	
6th recovery minute DPR				
Intercept	0.478(0.210)	0.741	0.449(0.499)	0.675
Age (years)	0.006(0.002)			
HRp (b/min)	0.006(0.001)		0.009(0.004)	
HRi (b/min)			0.013(0.006)	
Wp (Watt)	-0.006(0.001)		-0.014(0.002)	

Discussion

In normal people double (DP) product is increased with the increase of the workload, but this is only partially true in the presence of cardiovascular diseases. There are limited studies studying the DP during the exercise stress test.

Based on the fact that heart rate and blood pressure responses to exercise are triggered by the workload, we think that also that their decrease during recovery is directly connected to the workload and not to the peak heart rate or blood pressure levels. The same logic can be applied to DB, which is mathematically derived by the above measures. So we assume that if the variation of the DP is provoked by the workload during exercise and the recovery, these can be better represented by the rates of the DB with the workload.

In males with normal blood pressure, DP in rest does not show important changes even in the presence of coronary artery disease, however, their peak workload was significantly lower. It can be deduced that in normotensive males the workload is not the only factor that triggers the increase of DP. An important role is also played by the presence of coronary artery disease. The same is true also for the DB at the end of the first stage of exercise in this group of patients with or without coronary artery diseases.

On the other hand, the DP at the peak of the exercise is significantly lower in males with normal blood pressure and the presence of coronary disease. The same can be stated also for DP in the second, fourth, and sixth minutes of recovery.

Diversely from DP at the first stage of the exercise, the rate of DB to workload in the same stage of exercise is significantly higher in males with normal blood pressure and coronary artery disease. This shows that coronary artery disease is accompanied by an important decrease in the relative efficiency of the heart in the first stage of the exercise or in the submaximal effort.

Although the peak DP is clearly lower in males with normal blood pressure and CAD, the rate of DP to workload in the peak of exercise (DPRp) tends to be higher in this group of patients, although not statistically significant compared to those with normal coronary arteries. These findings can suggest that the relative efficiency of the heart in the peak of exercise in patients with CAD improves similarly to people with normal coronary arteries, but in a significantly lower level of exercise capacity.

Opposed to the fact that DP in the fourth minute of recovery is significantly lower in normotensive males with CAD, the DPR in this phase of recovery is significantly higher in this group of patients. This shows that the debt of myocardial oxygen is higher in patients with CAD and requires a longer time to balance its need. On the other hand, there might be other factors that mask the real decrease of the peak relative efficiency of the heart in these patients.

The above deductions are also supported by the results of DPR in the sixth recovery minute and are a further proof of the above correlations.

It also important to remember that in normotensive males with or without coronary disease the rates of DP to workload is not influenced by basic characteristics such as BMI, weight, height, and initial SBP and DBP.

Conclusion:

The values of DP in the peak exercise and during all the recovery phase are significantly lower in normotensive males with abnormal coronary angiography compared to those with normal coronary arteries and these findings can be used to detect the presence of coronary artery disease despite the ECG changes and they are not affected by the baseline characteristics of the patients.

The ratios between DP to the workload at the first stage, and at the end of the fourth and sixth minutes of recovery is significantly lower in normotensive male patients with coronary artery disease compared to those without CAD and can be independent predictive parameters for the disease.

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