RESEARCH ARTICLE

Rate Pressure Product Predicts Cardiovascular Risk in Type 2 Diabetics with Cardiac Autonomic Neuropathy

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ABSTRACT

Background: Unexplained sudden deaths due cardiac involvement are linked to autonomic neuropathy in diabetics but mechanisms remain unclear. Heart rate and pulse pressure etc have been used to predict cardiovascular risk. But the association of Rate Pressure Product remains unascertained.

Objective: To predict cardiovascular risk in type 2 diabetic patients with cardiac autonomic neuropathy using a non-invasive indicator, rate pressure product.

Materials and Methods: Case control study done on two groups of 20 each, age matched type 2 diabetics with/without cardiac autonomic neuropathy and matched with 20 controls of either sex (n=60). Rate Pressure Product was measured in response to cold pressor and hand grip test. Statistical analysis was done using SPSS software by paired and unpaired t test.

Results: There was a significant increase in rate pressure product in controls and in patients without autonomic neuropathy after the tests ($p<0.001$). Patients with autonomic neuropathy had non-significant increase in rate pressure product ($p>0.001$). The change in RPP (ΔRPP) was least in diabetics with autonomic neuropathy and significant in controls and non-neuropathy diabetics using unpaired t-test ($p< 0.05$). Resting RPP was recorded highest in diabetic autonomic neuropathy patients.

Conclusion: Heightened resting RPP and failure of Rate Pressure Product increment during cardiac sympathetic stimulation promotes aggravated ischemic episodes. This renders autonomic neuropathy diabetics vulnerable to adverse cardiovascular events leading to increased morbidity and mortality.

KEY WORDS: Rate Pressure Product; Autonomic Neuropathy; Diabetes Mellitus

INTRODUCTION

Autonomic neuropathy is a well-recognized complication of diabetes mellitus and its incidence has been reported to be 20%-40%.[1] Cardiac autonomic neuropathy causes abnormalities in heart rate control and central and peripheral vascular dynamics.

Many parameters have been used to predict cardiac risk. An elevated heart rate at rest is confirmed as an independent risk factor for sudden death in middle-aged men.[2] Pulse pressure has been used to predict cardiovascular risk in patients with type 2 diabetes mellitus.[3]

This study aimed to define and evaluate another parameter which was non-invasive and could be used to indicate/predict cardiac risk in diabetic cardiac autonomic neuropathy patients – the rate pressure product.

Rate Pressure Product is the product of heart rate and systolic blood pressure. It is an easily measurable index which correlates well with myocardial oxygen demand and defines the response of coronary circulation to myocardial metabolic demands.[4]

MATERIALS AND METHODS

Study was carried out on 60 subjects taken from DMC & H, Ludhiana. This study was a prospective study approved by the Institutional Review Board of our hospital. Blood pressure and heart rate were recorded in response to autonomic function tests (cold pressor test, hand grip test) and rate pressure product calculated from it. A rest interval of five minutes was given between the two tests assuming that the effect of first test is nullified within five minutes before application of the second test. Blood Pressure was recorded using sphygmomanometer and heart rate was calculated from lead II recorded on ECG machine (Cardiofax, Medicaid Systems). Statistical analysis was done using SPSS 7.0 statistical package for windows. Students paired and unpaired 't' test was applied. $P< 0.001$ and $p<0.05$ were taken as levels of significance

Age matched subjects of either sex were divided into three groups of 20 each.

Group A: Patients of type 2 diabetes with cardiac autonomic neuropathy. These patients were having a postural fall in BP > 30 mm Hg.[5]
Group B: Patients of type 2 diabetes without cardiac autonomic neuropathy. These patients did not show a postural fall in BP > 30 mm Hg.
Group C: Healthy subjects free from any systemic illness.

History and examination were recorded on a proforma. Informed written consent was taken from each subject before commencing the test. Type 2 diabetic subjects were examined to rule out Ischaemic Heart Disease, Congestive heart failure and Cardiac arrhythmias.

Cold Pressor Test: The baseline blood pressure (arm not immersed) and ECG of the subject were recorded. The subject was asked to immerse his non dominant hand up to the wrist[6] crease in cold water held at four degree Celsius.[7] ECG was being recorded simultaneously. The recording of blood pressure was made at the pain threshold i.e. the interval between the immersion of hand to the subjective feeling of pain[8] (with hand immersed in cold water) or at two minute[9] interval in patients with autonomic neuropathy who did not reach the pain threshold even after two minutes.

Hand Grip Test: The baseline blood pressure and ECG were recorded. The subject was asked to hold the hand grip dynamometer in the dominant hand with a 30% of maximum grip strength[10] for a period of three minutes.[11] ECG was being recorded simultaneously. The blood pressure was recorded just before the release of hand grip from the non-exercising arm.

Heart Rate Calculation: The heart rate was calculated from R- R interval recorded using limb lead II on ECG machine (cardiofax). The highest heart rate achieved was considered. Speed of paper was kept at 25mm/sec. Heart rate was calculated as follows:

$$Heart\ Rate = \frac{60 \times 125}{RR\ Interval} = \frac{1500}{RR\ Interval}$$

Rate Pressure Product Calculation: It is also known as Robinson Index.[12] It is a product of systolic blood pressure and heart rate. RPP = Systolic Pressure in mm Hg x Heart Rate in beats/min x 10^{-2} The value obtained is expressed as mm Hg. beats per min.10^{-2}[13]

RESULTS

Forty diabetics and twenty healthy controls with mean age of 53.65 ± 8.00, 52.05 ± 5.70 and 46.4 ± 6.17 years in group A, B & C respectively were selected for study. The average duration of diabetes in group A and group B was twelve and eight years respectively.

Rate Pressure Product was determined in response to cold pressor test and hand grip test in all the subjects and compared between the three groups. On subjecting to cold pressor test and hand grip test, the diabetic cardiac autonomic neuropathy patients (group A) had a non-significant change in RPP (Table 1) ($p>0.001$) after the test. Patients without autonomic neuropathy (group B) and the controls (group C) demonstrated a significant increase in RPP ($p < 0.001$) (Table 1) after the tests.

The change in RPP (ΔRPP) of the three groups was analysed amongst the groups using unpaired t test. It was found that ΔRPP in cardiac autonomic neuropathy patients was the lowest. The change in RPP when compared amongst the groups was non-significant between controls and diabetics with cardiac autonomic neuropathy ($p>0.05$) (Table 2).

Table-1: Results of Paired t - Test for Cold Pressor Test & Hand Grip Test

Test & Groups	COLD PRESSOR TEST			HAND GRIP TEST		
	Groups RPP (mm Hg.bpm.10-2)					
	Group A	Group B	Group C	Group A	Group B	Group C
Mean ± SD (before test)	121.62±19.068	117.69±18.630	99.13±15.053	122.17±18.703	115.04±16.257	98.77±16.607
95% CI	112.69 – 130.54	108.98 – 126.41	92.09 – 106.18	113.41 – 130.92	107.44 – 122.65	90.999 – 106.54
Mean ± SD (after test)	121.96±19.036	142.44±21.493	123.33±22.126	122.27±18.55	142.57±24.612	120.01±21.762
95% CI	113.05 – 130.87	132.38 – 152.50	112.87 – 133.58	113.59 – 130.95	131.06 – 154.08	109.83 – 130.198
p – value	0.33^{NS}	0.000000347*	0.00000241*	0.33^{NS}	0.00000433*	0.0000000138*

*p<0.001; NS – non significant; Group A - diabetics with cardiac autonomic neuropathy; Group B - diabetics without cardiac autonomic neuropathy; Group C - controls

Table-2: Comparison of Change in Rate Pressure Product (Δ RPP) between the Groups using unpaired t - Test

Δ RPP(CPT)(mm Hg.bpm.10^{-2})	Mean ± SD	p - value	95 % CI
Δ RPP 1	24.09 ± 16.25	0.894 NS	16.49 – 31.70
ΔRPP 2	24.75 ± 14.54		17.94 – 31.55
Δ RPP 1	24.09 ± 16.25	0*	16.49 – 31.70
Δ RPP 3	0.34 ± 1.54		- 0.38 – 1.07
Δ RPP 2	24.75 ± 14.54	0*	17.94 – 31.55
Δ RPP 3	0.34 ± 1.54		- 0.38 – 1.07
Δ RPP(HGT) (mm Hg.bpm.10^{-2})	**Mean ± SD**	**p – value**	**95%CI**
Δ RPP 4	21.24 ± 10.09	0.221 NS	16.52 – 25.96
ΔRPP 5	27.49 ± 19.92		18.45 – 36.60
Δ RPP 4	21.24 ± 10.09	0*	16.52 – 25.96
Δ RPP 6	0.10 ± 0.46		- 0.11 – 0.32
Δ RPP 5	27.49 ± 19.92	0*	18.45 – 36.60
Δ RPP 6	0.10 ± 0.46		- 0.11 – 0.32

NS – non significant; * ($p < 0.05$) ΔRPP1 - Change in RPP in controls; ΔRPP 2 - Change in RPP in diabetics without cardiac autonomic neuropathy; ΔRPP 3 - Change in RPP in diabetics with cardiac autonomic neuropathy; ΔRPP 4 - Change in RPP in controls; ΔRPP 5 - Change in RPP in diabetics without cardiac autonomic neuropathy; ΔRPP 6 - Change in RPP in diabetics with cardiac autonomic neuropathy; CPT Cold Pressor Test, HGT Hand Grip Test

DISCUSSION

On exposure to sympathetic stimulation during stressful episodes of any type (cold water in case of cold pressor test and isometric exercise in the case of hand grip test), the heart rate and blood pressure rises significantly. Rate Pressure Product being a product of systolic blood pressure and heart rate is expected to rise. Cardiac autonomic neuropathy patients did not show a significant increase in rate pressure product (group A) ($p>0.001$) after the tests. This was because a sympathetic dysfunction was present in such patients. A similar result by Khoshdel, et al, demonstrated that diabetics had an impaired change in heart rate, systolic blood pressure and diastolic blood pressure in response to exercise.[14]

Patients without cardiac autonomic neuropathy (group B) had a significant increase in rate pressure product after the tests. This could be because a complete sympathetic dysfunction was not yet present in these patients. The control group (group C) showed a significant increase in rate pressure product after the tests. This is an expected result as controls were healthy volunteers free from any disease with a well functioning autonomic nervous system.

RPP is an indicator of myocardial blood flow. Sympathetic stimulation increases myocardial metabolic demand. This can only be met by increasing the coronary blood flow (indirectly seen as increase in RPP represented as ΔRPP). The change in rate pressure product (ΔRPP) was lowest in diabetics with cardiac autonomic neuropathy. These results suggest an uncoupling between myocardial metabolic demand and supply in diabetic cardiac autonomic neuropathy patients when subjected to sympathetic stimulation/stress. Failure of Rate Pressure Product to increase to meet the body demands at times of physical and emotional stress makes such patients vulnerable to adverse cardiovascular events.

The inverse association of Rate Pressure Product to hemodynamic response supports the early development of arterial and ventricular stiffness in Diabetes Mellitus, unrelated to other likely risk factors such as hypertension and hyperlipidemia. This renders diabetic autonomic neuropathy patients vulnerable to various cardiac risks like left ventricular dysfunction, cardiac arrhythmias, silent myocardial infarction, cardiac arrest and sudden death on exposure to current life stress episodes.

Another observation of the study was that the resting RPP was found to be highest (mean >120) in cardiac autonomic neuropathy patients. Since already RPP at rest was high, so there was little capacity of the body to increase it further and improve myocardial perfusion. Disturbance in sympathovagal balance could be the cause of increased baseline rate pressure product especially if parasympathetic injury is predominant A study in London confirmed independent association of diabetes with RPP which was estimated to be 9% higher than in patients without diabetes and found that diabetes showed an independent association with heightened rate pressure product which itself was significantly associated with development of heart failure.[15] Some investigators have observed that angina pectoris occurs at a constant value of RPP and that the degree of ST segment depression is correlated with RPP. Thus the risk of cardiovascular problems increases with greater levels of RPP.[16]

Thus, a simple measurement of a resting rate pressure product and a change in rate pressure product in response to cardiac sympathetic stimulation can give a clue towards the status of myocardial blood flow in such patients. This can hence be used as a simple non-invasive predictor of cardiovascular risk in such patients.

Thus, we tend to promulgate RPP as an additional valuable marker predicting morbidity and mortality in patients of autonomic neuropathy especially when exposed to times of increased myocardial demand like exercise, mental, emotional stress or cold exposure.

CONCLUSION

A non-invasive index, Rate Pressure Product, can predict cardiovascular risk in diabetic cardiac autonomic neuropathy patients. Resting RPP as well as change in RPP give a clue towards coronary perfusion status. Future studies with more number of patients will help to further highlight the role of rate pressure product in predicting the extent of cardiac risk in such patients.

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