EFFECT OF DIABETIC AUTONOMIC NEUROPATHY ON DETERMINANTS OF MYOCARDIAL OXYGEN DEMAND

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Abstracts: **Background:** Resting myocardial oxygen demand determinants are less studied in diabetic autonomic neuropathy patients. **Objective**: An insight into the determinants of myocardial oxygen demand in diabetic autonomic neuropathy patients may explain sudden adverse cardiovascular events in such patients. **Methods**: Case control study (n=60) was done on forty age matched (40-60 yr) type 2 diabetics with/ without diabetic cardiac autonomic neuropathy and twenty controls for myocardial oxygen demand determinants (heart rate, rate pressure product, systolic blood pressure) at rest. **Results**: Results demonstrated (unpaired't' – test, 'SPSS' software) that all variables were significantly increased in neuropathy patients compared to controls ($p<0.05$) (95%CI). Heart rate, rate pressure product significantly increased in neuropathy patients compared to non-neuropathy counterparts ($p<0.05$) (95%CI). Significantly increased heart rate, rate pressure product in non-neuropathy patients compared to controls ($p<0.05$)(95%CI). Resting rate pressure product highest (>12) in neuropathy patients. **Conclusion**: Diabetic cardiac autonomic neuropathy significantly increases all determinants of resting myocardial oxygen demand contributing to exaggerated ischemic episodes and increased mortality even at rest.

Key Words: Myocardial oxygen demand, Diabetic autonomic neuropathy, determinants of myocardial oxygen demand.

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Introduction:

Dysfunction of the autonomic system predicts cardiovascular risk and sudden death in patients with type 2 diabetes. It also occurs in prediabetes, providing opportunities for early intervention[1]. The exact mechanisms remain unclear.

A relative hyperadrenergic tone is suspected[2]. The earliest manifestations of autonomic neuropathy in diabetes tend to be associated with parasympathetic denervation[2].

Autonomic dysfunction affects resting heart rate and blood pressure. It is however accepted that a fixed heart rate that is unresponsive to moderate exercise, stress, or sleep indicates almost complete cardiac denervation and is indicative of advanced Cardiac Autonomic Neuropathy[3].

Few studies in English peer reviewed literature have tried to observe the determinants of resting myocardial oxygen demand in diabetic autonomic neuropathy patients which could be possibly involved in understanding silent adverse cardiovascular events occurring in this subset of patients.

This study was undertaken to determine the potential of diabetic cardiac autonomic neuropathy to influence resting myocardial oxygen demand in this part of the world.

Material and Methods:

Study was done on total 60 subjects of either sex between 40 – 60 years taken from a tertiary health care centre in North India - 40 diabetics with duration of diabetes of 8-12 years and 20 healthy controls.

Variables for myocardial oxygen demand (heart rate, systolic blood pressure and rate pressure product) were considered.

Resting Blood pressure and heart rate were recorded and rate pressure product calculated in the subjects.

This study was approved by the Institutional Ethical Committee of our Hospital.

Details of history and examination were recorded on a proforma. Consent was taken from all subjects before the recording.

Fasting / Random blood sugar was performed using glucometer.

They were divided into 3 groups of 20 subjects each.

Group A: Patients having type 2 diabetes with clinically evident autonomic neuropathy. (postural fall in systolic BP > 30 mm Hg, cardiac involvement assessed as impaired response to hand grip .[4]

Group B: Patients without diabetic cardiac autonomic neuropathy.

Exclusion Criteria for patients: Ischemic Heart Disease, Congestive heart failure and Cardiac arrhythmias. Patients on α blockers, β blockers, calcium channel blockers, diuretics, antiarrhythmics, antipsychotics were excluded from study.

Group C: 20 healthy age-matched controls were taken. Resting blood pressure and heart rate were recorded in all the subjects supine, at complete physical and mental rest.

Blood Pressure was recorded using sphygmomanometer.

Heart rate was calculated from lead II on cardiofax ECG machine (Medicaid Systems).

$$\text{Heart rate} = \frac{60 \times 25}{\text{R-R interval}} = \frac{1500}{\text{R-R interval}}$$

Rate Pressure Product was calculated as a product of heart rate and systolic blood pressure. [5]

RPP = Systolic Pressure in mm Hg x Heart Rate in beats/min x 10^{-3}

Statistical unpaired't' - test was done using SPSS software with statistical significance set at $p < 0.05$.

Result:

Results using unpaired t' – test demonstrated that all variables were significantly high in group A compared to group C whereas only heart rate and rate pressure product were significantly high in group A compared to group B ($p<0.05$)(95%CI). Group B observed significantly heightened heart rate and rate pressure product compared to group C ($p<0.05$)(95%CI).

The resting rate pressure product was highest (>12) in diabetic autonomic neuropathy patients.

Table 1: Results of unpaired t-test for group A and group C

Variable	Group A Mean ± SD	95% Confidence Intervals	Group C Mean ± SD	95% Confidence Intervals	p-value
SBP	129±7.18	125.64 – 132.36	120.4±9.97	115.74 – 125.06	0.003*
HR	100.48±10.31	95.66 – 105.31	82.37±10.81	77.31 – 87.43	0*
RPP	12.99±1.31	12.38 – 13.61	9.91±1.50	9.21 – 10.62	0*

*($p<0.05$)

SBP= systolic blood pressure (mm Hg)HR= heart rate (beats/min)RPP= rate pressure product (mm HgX beats per min/1000)

Table 2: Results of unpaired t-test for group B and group C

Variable	Group B Mean ± SD	95% Confidence Intervals	Group C Mean ± SD	95% Confidence Intervals	p-value
SBP	127.20± 14.03	120.63 – 133.77	120.4 ±9.97	115.74 – 125.06	0.085^{NS}
HR	92.35±8.81	88.22 – 96.47	82.37 ±10.81	77.31 – 87.43	0.003*
RPP	11.77±1.86	10.90 – 12.64	9.91± 1.50	9.21 – 10.62	0.001*

*($p<0.05$)
NS-Non significant

SBP= systolic blood pressure (mm Hg) HR= heart rate (beats/min)RPP= rate pressure product (mm HgX beats per min/1000)

Table 3: Results of unpaired t-test for group A and group B

Variable	Group A Mean ± SD	95% Confidence Intervals	Group B Mean ± SD	95% Confidence Intervals	p-value
SBP	129±7.18	125.64 – 132.36	127.20±14.03	120.63 – 133.77	0.612[NS]
HR	100.48±10.31	95.66 – 105.31	92.35 ±8.81	88.22 – 96.47	0.011*
RPP	12.99 ±1.31	12.38 – 13.61	11.77 ±1.86	10.90 – 12.64	0.021*

*(p<0.05)

NS – Non Significant

SBP= systolic blood pressure (mm Hg)HR= heart rate (beats/min)RPP = rate pressure product (mm HgX beats per min/1000)

Table 4: Resting Rate Pressure Product in subjects

RPP	Group A	Group B	Group C
(Mean ± SD)	12.99±1.31	11.77±1.86	9.91±1.50

RPP =rate pressure product (mm HgX beats per min/1000)

Discussion:

The present study was carried out with the aim to determine the potential of diabetic cardiac autonomic neuropathy to influence determinants of resting myocardial oxygen demand.

Variables for myocardial oxygen demand (heart rate, systolic blood pressure and rate pressure product) were recorded in age matched diabetics with and without diabetic cardiac autonomic neuropathy and controls.

A significantly elevated resting heart rate was observed in group A compared to group B & C (p<0.05) (Table 1,2,3). The highest resting heart rates were observed in group A. This could probably be due to cardiac parasympathetic impairment. Resting heart rates of 90-100 beats per minute and occasional heart rate increments upto 130 beats per minute occur[6]. The highest resting heart rates have been found in patients with parasympathetic damage, occurring earlier in the course of cardiovascular autonomic neuropathy than sympathetic nerve dysfunction: in those with evidence for combined vagal and sympathetic involvement, the rate returns toward normal but remains elevated. A fixed heart rate that is unresponsive to moderate exercise, stress or sleep indicates almost complete cardiac denervation[6]. The relationship between autonomic damage and the duration of diabetes is not clear, although numerous studies (eg, Vinik et al) support an association[7].The time scale for the progression of subclinical CAN to the development of abnormal CART(cardiac autonomic reflex testing) is unclear; similarly the natural history of the development of early cardiac abnormalities (such as torsion or deficits in myocardial perfusion or cardiac energetic) and its relationship to subclinical CAN is also unclear. But we estimate that many patients with sub-clinical CAN will develop abnormal CART and early features of cardiac involvement within 5 years of developing abnormal frequency and time domain parameters[8]. A significantly elevated heart rate in group B compared to controls may be due to some subclinical form of autonomic neuropathy which is getting to start in such patients but is not clinically evident as yet. An elevated heart rate at rest was confirmed as an independent risk factor for sudden death in middle-aged men[9].

Systolic blood pressure was significantly high in group A compared to group C (p<0.05) (Table 1).

According to JNC VI - recommended values of blood pressure are 130/85 mm Hg in individuals with kidney disease or diabetes[10,11].

Though the subjects chosen met the above criteria, but still significantly higher values were obtained. This could be explained by a study conducted by Istenes I, et al, who found that subjects with diabetic autonomic dysfunction with no history of hypertension and normal clinic blood pressure values, had significantly higher 24 hour mean systolic blood pressure, systolic blood pressure load and hyperbaric impact values compared with those with normal autonomic function as well as with healthy counterparts[12].

Diabetic cardiac autonomic neuropathy patients had a significantly higher Rate Pressure Product at rest compared to non-neuropathy counterparts as well as controls ($p<0.05$) (Table 1,2,3). Resting tachycardia and significantly elevated systolic blood pressure potentially contributed to significantly heightened resting rate pressure product. Group B patients also had significantly higher resting Rate Pressure Product compared to controls. Foo K, et al, confirmed independent association of diabetes with RPP which was estimated to be 9% higher than in patients without diabetes[13].

An interesting observation in the study was that resting rate pressure product was highest in cardiac autonomic neuropathy patients.

Pepper MG and Crawley BE have calculated mean normative values of RPP to be <12 (heart rate between 60–120 beats per minute and Systolic blood pressure between 100–140 mm Hg, RPP = HR X SBP/1000)[14]. The resting rate pressure product was found to be highest, out of normative range, (RPP >12) (Table 4) in diabetic autonomic neuropathy patients.

Conclusion: Therefore, we conclude that all the determinants of myocardial oxygen demand are significantly elevated in diabetic autonomic neuropathy patients compared to non neuropathy counterparts and controls even at rest. Only resting heart rate and rate pressure product are significantly elevated in diabetics without diabetic cardiac autonomic neuropathy.

Resting rate pressure product is highest in diabetics with cardiac autonomic neuropathy and values > 12 have been observed. Hence a type 2 diabetic with resting RPP converting from a value <12 towards a value >12 should be suspected of developing cardiac autonomic neuropathy.

Heightened myocardial oxygen demand at rest may be the potential agent aggravating regional myocardial ischemia leading to adverse cardiovascular events occurring in such patients even at rest.

Limitations of the study include lesser number of patients taken.

Individual studies on patients with selective sympathetic/parasympathetic impairment should be conducted to make the mechanisms of adverse cardiovascular events more clear. Further research to elaborate the extent of such risk is required.

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