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ORIGINAL ARTICLE

The occurrence of clinically evident ischaemic heart disease in patients of type 2 diabetes with resting tachycardia

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ABSTRACT

Background: Epidemiological studies have reported the association between resting tachycardia (RT) and cardiovascular mortality, both in cardiac and non cardiac subjects.
Aims: To investigate the association between RT and clinically evident ischaemic heart disease (IHD) in diabetic patients.
Settings and Design: Retrospective analysis of the hospital data.
Data collection period - 2008-2009.
Material and Methods: Electro cardiogram recordings of diabetic patients (n=100) were used for the calculation of the resting heart rate (RHR). RHR > 90 beats/ minute (bpm) was considered as RT. Presence/ absence of IHD were noted from the patient case records. The association between RHR and the prevalence of IHD was analyzed by applying the x^2 test by using the SPSS software 12 version. P values <0.05 were considered to be statistically significant
Results: Fifteen percent of the patients had RT and 28 % had clinical evidence suggestive of IHD. More than 50 % of those with RHR >90/bpm had IHD as compared to 23.5% in the group having RHR ≤90/bpm and the comparison between the two showed statistical significance (p=0.028).
Conclusions: This retrospective analysis reports a positive association between RT and the pre-existing IHD in diabetic patients. RHR could be considered as a clinical marker for clinically evident IHD. A careful search for coronary artery disease, including the administration of an angiogram need to be considered in all diabetic patients presenting with RT.

Key Words: Cardiac autonomic neuropathy, Diabetes mellitus, Ischaemic heart disease, resting heart rate, resting tachycardia.

Key Messages:

1. The prevalence of clinically evident ischaemic heart disease is two fold higher in diabetics with resting tachycardia than in those without resting tachycardia.
2. All diabetic patients presenting with resting tachycardia, even those without a clinical evidence of ischaemic heart disease, need to undergo a careful search for the presence of coronary artery disease.
3. Such a diagnostic approach may help to prevent the attacks of myocardial infarction or sudden cardiac deaths in diabetic patients.
4. Heart rate lowering therapy using sympatholytics, calcium channel blockers and selective I_f inhibitors may be of value in all diabetic patients with resting tachycardia.

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Patients of type 2 diabetes mellitus (T2DM) are reported to have an increase in all-cause mortality and elevated resting heart rate (RHR) is associated with an increased risk of death due to cardiovascular, cardiac and ischaemic heart disease (IHD) among patients of T2DM [1]. Resting tachycardia (RT) was considered as a mere indicator of cardiovascular risk until several epidemiological studies unveiled an independent association of RT with cardiovascular and all cause mortality in the population with or without the evidence of pre-existing coronary artery disease (CAD) and now, RT is regarded as one of the independent cardiovascular disease risk factors (CVDRF) [2]. HR reduction has proven to be beneficial in myocardial infarction (MI), chronic heart failure (CHF) and in stable angina pectoris [2]. However, HR lowering is not considered for the treatment of the general population without CVD. Although, there exists a large number of studies that relate mortality with RT, published data associating RT with the occurrence of IHD is limited. This hospital-based retrospective analysis was aimed at investigating the association between RT and the presence of clinically evident IHD in patients of T2DM.

Material and Methods

We used the secondary data of T2DM patients (n=100) who had participated in an institutional ethics committee approved research project and all these subjects were the registered members of the hospital diabetic clinic. The study participants had their 12 lead electrocardiograms (ECG) recorded in the morning, following ten minutes of rest, one hour after breakfast. The necessary medications were taken by the patients, half an hour before breakfast._ The participants were asked to refrain from smoking and from having hot beverages half an hour before the ECG recording. Those with poor glycaemic control, acute diabetic complications, infection, or acute coronary syndrome within last six months, were excluded. The blood pressure was stabilized before entry into the study in hypertensive patients. RHR was obtained automatically from the ECG recording. RHR >90beats per minute (bpm) was defined as RT. The criteria followed to define the presence of clinically evident IHD are - a medical history of angina with or without ECG or stress test findings of ischaemia; unstable angina or a documented history of myocardial infarction with supportive findings in ECG, stress test, echocardiography and cardiac enzymes. Asymptomatic CAD cases were also considered for analysis. Stable angina and asymptomatic CAD were grouped as category 1, whereas category 2 included cases of unstable angina and MI. The demographic data, body-mass index (BMI), fasting blood glucose (FBG), HbA1c, co-morbid conditions, complications of DM and the list of medications, all as on the day of ECG recording, were documented. The variables were presented either as percentage values or as mean±SD, as in case of continuous variables. The association of RHR with IHD and with other variables like gender, BMI, co-morbidities and with the use of different drugs were analyzed by applying the x^2 test by using the SPSS software 12 version. P values <0.05 were considered to be statistically significant.

Results

Table 1 depicts the patient characteristics. The association between the frequency of IHD and RHR is presented in Table 2. Fifteen percent of patients had RT and 28 % had clinical evidence suggestive of IHD. Five among the latter had MI, none having undergone coronary intervention. More than 50 % of those with RHR >90/bpm had IHD, as compared to 23.5% in the group having RHR ≤90/bpm and this association is of statistical importance (p=0.028). HR was not significantly related with (data not shown) gender, BMI (<25 & ≥25kg/m^2), presence / absence of co-morbidities (hypertension, and dyslipidaemia) and peripheral neuropathy (as diagnosed by history, clinical

examination and biothesiometry for vibration threshold) and with the use of different drugs (insulin, oral anti diabetic drugs, beta blockers, calcium channel blockers and drugs modulating rennin - angiotensin system).

Discussion and Conclusions

In this retrospective analysis, a strong positive association between RT and the pre-existing IHD was demonstrated in diabetic patients. The RT group had a two fold higher frequency of IHD than the group with RHR ≤90bpm. Several epidemiological studies have reported a strong association between RT and an all-cause and cardiovascular mortality in the population, with various CVDs [2],[3],[4]. Interestingly, elevated RHR was also considered as an independent predictor of an all-cause and cardiovascular mortality in epidemiological follow-up studies that included healthy individuals [5]. In postmenopausal women without baseline CAD, RHR was found to be a predictor of coronary events [6]. In another study, elevated RHR was found to be an independent risk factor for fatal IHD events, but particularly for sudden cardiac death and this effect was marked in men who were free of pre-existing IHD at initial examination [7]. The role of RHR in myocardial ischaemia as seen in patients with stable angina is well known. Increased HR contributes to an imbalance between myocardial oxygen demand and supply, by causing both an increase in myocardial oxygen demand and a decrease in coronary blood supply, the latter resulting from a reduction of collateral perfusion pressure and collateral flow [5]. Although the present analysis did not demonstrate a positive relation of RT with pre-existing hypertension or dyslipidaemia, research has revealed a significant association of RT with hypertension and an atherogenic lipoprotein profile, the two well known CVDRFs [8]. Experimental studies in monkeys suggest that high HR can also exert a direct atherogenic action on the arterial wall due to haemodynamic stress on the vascular wall and reduction in the HR retarded the development of coronary atherosclerosis. Haemodynamic stress related to high HR can also encourage the disruption of the atherosclerotic plaque and precipitate an acute coronary event [8]. Clinical trial data report that the currently existing HR lowering drugs significantly reduced the cardiovascular events in subjects with acute MI and CHF and that HR reduction itself was partly attributed for the favourable outcomes [2]. HR reduction is the cornerstone of the treatment of chronic stable angina [2], although the beneficial effects of HR reduction in hypertension is debated [9]. Despite the epidemiological evidence on the predictive role of RHR in the mortality in the CVD and the non CVD population, RHR has not been given importance in CVD risk assessment [2]. HR lowering is approved for the therapy of clinically evident IHD as a secondary prevention strategy and not for the primary prevention of IHD in the non-cardiac general population presenting with RT. This is probably because there is no substantial evidence on the predictive role of RT in the incidence of IHD and on the beneficial effects of HR lowering drugs in decreasing the incidence of IHD in subjects with RT.

A large follow-up study confirmed that in patients of T2DM, elevated RHR is associated with an increased risk of death due to cardiovascular, cardiac and IHD [1]. Cardiac autonomic neuropathy (CAN), one of the common complications of T2DM, is found to be linked with RT, painless myocardial ischaemia or infarction and sudden cardiac deaths [10],[11],[12]. The mortality rate is higher for diabetics with CAN than for those without CAN and silent ischaemia is significantly more frequent in patients with, than in those without CAN, which possibly delays appropriate therapy. The sympathetic nervous system is stimulated in the early stages of DM and extended exposure of the adrenergic receptors to increased catecholamine levels, together with hyperglycaemia and insulin deficiency, is believed to cause diabetic CAN [11]. In the present study, the lack of clinical assessment data on CAN does not facilitate us to link CAN and RT. Even in the absence of CAN, sympatho adrenal discharge consequent to hypoglycaemia alone, can add to the risk of ventricular tachycardia and death [13]. However, the mean FBG (145.44±38.04mg/dl) measured prior to recording ECG in our study ruled out the possibility of incident hypoglycaemia as the causal factor for RT. Epidemiological studies have discovered an association between insulin

resistance syndrome (IRS) and an increase in the sympathetic activity, which was also supported by experimental evidence [8]. Insulin resistance is one of the key factors which is responsible for hyperglycaemia in T2DM and can result in a cluster of CVDRFs that constitute IRS and the risk of cardiac events is increased in the presence of IRS, even without overt DM [14].

Overall, evidence shows that RT plays an important role, either as a marker of excess sympathetic activity or as an independent risk factor in DM associated CVD risk. With this background highlighting the relevance of RT in DM, the findings of the present study that RT doubles the risk of developing IHD in diabetic patients, tempt us to opine that RHR could be considered as a clinical marker for clinically evident IHD. A careful search for CAD, including the application of an angiogram, need to be considered in all DM patients presenting with RT, even in those without symptoms which are suggestive of IHD. This strategy may be of great value in preventing attacks of MI or sudden cardiac deaths in DM patients. The results of the current analysis also prompt us to propose that HR reduction may be considered as a primary prevention measure for IHD in all diabetic patients with RT. With the available evidence, one can speculate that the pharmacological modulation of sympathetic activity aiming at reducing RHR in diabetics may decrease the incidence of IHD, not only by decreasing the oxygen demand, but also indirectly by preventing the progression of CAN and IR.

Although recording HR is a simple procedure, several practical problems can arise while aiming at an optimal HR on an individual basis with drugs, especially in a patient without established CVD [2],[3],[4],[5]. Moreover, in the absence of any evidence on the beneficial effects of HR reduction in preventing the subsequent IHD in an apparently non cardiac patient, our suggestion to consider HR lowering therapy for the primary prevention of IHD in this population may sound too premature. In addition, the present study had potential limitations. The subjects with current ECG reading were retrospectively evaluated for the presence or absence of IHD and hence, the association of current RHR was demonstrated with the prevalent IHD. This association was not adjusted for gender, BMI, co-morbid conditions, peripheral neuropathy and drug treatments, although, the independent association of HR was ruled out with these confounders.

Well designed prospective studies in a cohort of diabetic population need to be carried out to ascertain the predictive value of RHR for a new onset of clinically evident IHD in diabetic patients and to investigate the beneficial effects of currently existing HR lowering drugs like sympatholytics and non-dihydropyridine calcium channel blockers and a new class of pure HR lowering agents like selective I_f inhibitors (ivabradine). The outcome of such studies would help to draw primary preventive HR lowering treatment strategy guidelines for the diabetic population.

(Table/Fig 1) Patient characteristics

bpm =beats per minute ; IHD=Ischemic heart disease; IHD Category 1 = Stable angina & asymptomatic coronary artery disease; IHD Category 2=Unstable angina & myocardial infarction; DMRAS-Drugs modulating rennin-angiotensin system ; FBG-fasting blood glucose; BMI-body-mass index;

Variables	Values
Age (mean ± SD) years	60.59±10.2
Male: Female	54:46
Heart Rate bpm (mean ±SD)	78.33±12.33
Heart Rate>90 bpm (frequency)	15%
(mean ± SD)	95.80 ± 4.52
Heart Rate < 90 bpm (frequency)	85 %
(mean ± SD)	75.24 ±10.51
IHD (absent : present)	72:28
IHD Category 1	13/ 28
IHD Category 2	15/28
Dyslipidemia (absent: present)	72:28
Hypertension (absent: present)	60:40
Peripheral Neuropathy (absent: present)	77:23
Beta blocker use (absent: present)	81:19
Insulin use (absent: present)	64:36
Oral anti diabetics (absent: present)	19:81
Calcium channel blocker (absent: present)	80:20
DMRAS (absent: present)	74:26
HbA1c % (mean ±SD)	8.41±1.35
FBG mg/dl (mean ±SD)	145.44±38.04
BMI kg/m^2((mean ±SD)	25.15±2.81

(Table/Fig 2) Frequency of IHD among two heart rate groups

IHD	Heart Rate bpm		Total
	?90	>90	
Absent	65(76.5)	07 (47)	72
Present	20(23.5)*	08 (53)*	28
Total	85 (100)	15(100)	100

(Values within the parenthesis represent %)
*Comparison statistically & clinically significant, p=0.028 by Fisher's Exact Test

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