

Delayed Heart Rate Recovery and Exaggerated Blood Pressure Response during Exercise Testing in Nigerian Normotensive Diabetics

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Authors' contributions

This work was carried out in collaboration between all authors. Author EAA designed the study, wrote the protocol and the first draft of the manuscript. Author ATO was involved in study design and managed the literature searches. Author AOA performed the statistical analysis and was involved in writing the final draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The aim of this study was to identify the clinical profile of normotensive Type 2 diabetes mellitus (T2DM) with exercise related exaggerated systolic blood pressure (ESBP) and delayed heart rate recovery (HRR); and explore if there is relationship between ESBP and delayed HRR in them.

Materials and Methods: A total of 67 normotensive T2DM subjects underwent symptom limited maximal treadmill exercise using Bruce protocol. ESBP was defined as a peak exercise systolic blood pressure (BP) ≥ 210 mmHg in men and ≥ 190 mmHg in women. HRR was defined as the difference in HR from peak exercise to 1 min in recovery; delayed HRR was defined as ≤ 12 beats/min. Parameters of 36 subjects with ESBP were then compared with those of 31 subjects without ESBP.

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Results: There were 36 (53.7%) of the subjects with ESBP. Subjects with ESBP response had higher BMI, 2-hours post-prandial plasma glucose, resting SBP and DBP. Of those with ESBP, 41.7% were males and 58.3% were females ($X^2=8.75$, $P=0.003$). HRR was lower in subjects with ESBP compared with those without (23.00 ± 12.18 vs 38.55 ± 22.69 beats/minute; $P=0.001$). The presence of abnormal HRR was 30.6% in subjects with ESBP response compared with 9.7% in subjects without ($X^2=4.39$, $P=0.036$).

Conclusion: ESBP response to exercise is present in more than half of normotensive diabetics and about a third of those patients with ESBP have delayed HRR. Imbalance in the autonomic nervous system, probably heightened sympathetic nervous system, may be responsible for these pathologies.

Keywords: Normotensive diabetes mellitus; exaggerated blood pressure; heart rate recovery.

ABBREVIATIONS

CVD : Cardiovascular diseases
DBP : Diastolic blood pressure
ESBP : Exaggerated systolic blood pressure
HRR : Heart rate recovery
LVMl : Left ventricular mass index
SBP : Systolic blood pressure
T2DM : Type 2 diabetes mellitus

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is associated with loss of both sympathetic and parasympathetic innervation to the heart, otherwise referred to as cardiac autonomic neuropathy, and characterized by postural hypotension, cardiac denervation leading to a loss of an exercise or stress-induced heart rate rise, impaired systolic and diastolic function and changes in blood pressure. Blood pressure variability and the normal nocturnal dip in pressure are lost in diabetic autonomic neuropathy, leading to an increased average blood pressure and relative nocturnal hypertension [1] and this may increase cardiovascular risk. Other indices which may reflect autonomic neuropathy include increased QT dispersion in these patients and reduced heart rate variability [2,3].

Both exaggerated systolic blood pressure (ESBP) and delayed heart rate recovery (HRR) are exercise testing parameters that also have prognostic implications. HRR has been identified as a powerful and independent predictor of cardiovascular and all cause mortality in healthy adults [4], and in those with CVD including diabetes [5,6]. In like manner, ESBP response to exercise is associated with a 2-3 times greater risk of future development of hypertension [7] and a greater prevalence of left ventricular

hypertrophy [8] in otherwise normotensive individuals.

The two arms of the autonomic nervous system have reciprocal behaviors during incremental exercise. During exercise, there is activation of the sympathetic activity and parasympathetic withdrawal suggesting that BP and heart rate increments during exercise are related to stimulation of the sympathetic nervous system. However, during recovery, there is reactivation of the parasympathetic activity and subsequent withdrawal of the sympathetic activity.

An ESBP response to exercise has been thought to be related to excess stimulation of the sympathetic nervous system [9] while HRR after dynamic exercise is considered to be a function of vagal reactivation with the sympathetic withdrawal becoming more important later in recovery. Hence, delayed HRR is an abnormal heart rate response that may reflect a reduction in vagal tone [10] or an exaggerated sympathetic activation [11].

Previous studies have shown that reduced HRR is associated with type 2 diabetes [12]. Karavelioglu et al. [13] found that ESBP response to exercise was more frequent in normotensive diabetic patients compared with normotensive- non diabetic individuals.

There is paucity of data on these important prognostic indices in normotensive diabetic patients in Nigeria. This study, therefore, is aimed at identifying the clinical profile of normotensive T2DM with exercise related ESBP and delayed HRR; and explore if there is relationship between exercise related ESBP and delayed HRR in the same population of patients. Exaggerated systolic blood pressure response (ESBP) was defined as a peak exercise systolic blood pressure (BP) ≥ 210 mmHg in men and

≥ 190 mmHg in women [14]. HRR was defined as the difference in HR from peak exercise to 1 min in recovery [5]. Delayed HRR was defined as ≤ 12 beats per minute [5].

2. MATERIALS AND METHODS

This is a descriptive, hospital –based study with a study population consisting of 67 consecutive normotensive T2DM (male = 39; female = 28) seen at the cardiac laboratories of Obafemi Awolowo University Teaching Hospitals Complex, Ile Ife and Ekiti State University Teaching Hospital, Ado Ekiti, both in southwest Nigeria.

Demographic parameters of subjects were noted and recorded. All subjects were clinically examined to evaluate their body mass index (BMI) and cardiovascular status at rest. Subjects were considered diabetic if they had fasting plasma sugar (FBS) >126 mg/dl (7.0 mmol/l) [15] or if they were on hypoglycemic medication. FBS and 2-hour postprandial plasma glucose were obtained 24 hours prior to the procedures. Resting 12-lead electrocardiogram (ECG) was done to exclude patients with baseline ST-segment abnormalities and bundle branch block. Also excluded were patients with coexisting hypertension or who were on antihypertensive(s), established chronic kidney disease or serum creatinine >1.5 mg/dl (132 μ mol/l), congestive heart failure, valvular heart disease, and other diseases known to influence left ventricular (LV) function such as thyroid disease and severe obesity. All the subjects underwent treadmill symptom limited maximal exercise using Bruce protocol [16]. The protocol continued until one of several endpoints was reached. These included if the patient requested that the exercise be terminated; developed severe chest pain, fatigue, leg discomfort or dyspnea; developed frequent premature ventricular beats, developed a systolic blood pressure (SBP) >250 mmHg or a drop in the pretest SBP >10 mmHg; or developed any other reasons necessitating termination of exercise. All participants also had 2D echocardiography to determine left ventricular mass index according to standard procedures.

The HRR parameters were compared with respect to occurrence of ESBP or otherwise. Mean values of systolic and diastolic BP at baseline, peak exercise, left ventricular mass index and some other clinical and biochemical parameters were also compared with respect to occurrence of ESBP response.

Ethical clearance for the study was approved by the Ethics and Research Committee of the hospital in conformity with ethical guidelines of the 1975 Declaration of Helsinki and all the participants gave written consent to participate.

SPSS version 20.0 software (SPSS, Chicago, IL, USA) was used in the analysis of the data.

Continuous variables were expressed as mean \pm SD, while categorical variables were expressed as counts (percentages). Comparison between two groups was assessed by the Students t-test for independent variables, while the Chi-square analysis was used to compare proportions. P values <0.05 were considered statistically significant.

3. RESULTS

3.1 General

A total of 67 normotensive T2DM patients were seen comprising 39(58.2%) males. Mean age was 48.51 ± 8.20 years (males vs. females: 51.26 ± 6.71 vs. 44.68 ± 8.2 ; $P = 0.001$). Mean body mass index (BMI) was $24.61 \pm 3.43 \text{ kgm}^{-2}$. Females had significantly higher BMI compared to males (23.11 ± 2.14 vs. $26.7061 \pm 3.80 \text{ kgm}^{-2}$; $P < 0.0001$). Mean resting SBP, DBP and heart rate (HR) were 116.69 ± 6.28 mmHg, 72.39 ± 4.96 mmHg and 90.61 ± 13.41 beats per minute respectively. There was no statistically significant gender difference between mean resting SBP, DBP and HR among the study population.

3.2 Profile of Subjects with Exaggerated SBP

There were 36(53.7%) of the subjects with ESBP response to exercise. As shown in Tables 1 and 2, there was no significant mean age difference in the group with ESBP response compared to the group with normal BP response. Subjects with ESBP response had statistically higher BMI, 2-hours post-prandial plasma glucose, resting SBP and DBP. Of those with ESBP response, 41.7% were males and 58.3% were females ($X^2 = 8.75$, $P = 0.003$). Left ventricular mass index (LVMI) was abnormally high in 35.8% of the study population with 33.3% vs. 38.7% of subjects with ESBP and normal BP response, respectively ($P = 0.65$) having abnormally high LVMI.

Table 1. Clinical and exercise treadmill test profiles of the subjects according to the systolic blood pressure response

Variables	ESBP response	Normal SBP response	p value
Age (years)	49.22±4.24	47.68±11.16	0.44
BMI (kg ⁻²)	25.41±3.89	23.69±2.57	0.04
FBS ^{**} (mmol/L)	8.39 ±1.98	9.30±1.95	0.13
2HPP [#] (mmol/L)	14.68±2.62	11.16±1.94	<0.0001
HR ^Δ (/min)	90.36 ±17.38	90.90±6.56	0.87
SBP ^Δ (mmHg)	119.11±6.35	113.87±4.95	<0.0001
DBP ^Δ (mmHg)	73.67±6.33	70.90±1.74	0.02
Pulse pressure (mmHg)	45.44±8.73	40.97±5.43	0.18
LVMl [†] (gm ⁻²)	84.78±18.28	85.94±12.03	0.74
Peak SBP (mmHg)	211.11±17.03	191.61±7.79	<0.0001
Peak DBP (mmHg)	97.58±9.37	90.01±0.01	<0.0001
Peak HR (/min)	164.58±16.48	164.61±5.97	0.99
HR reserve	92.70±19.23	91.22±15.81	0.70
HR recovery	23.00 ±12.18	38.55±22.69	0.001
Recovery time	6.52±2.12	4.62±1.85	<0.0001

BMI - Body mass index; FBS^{**} - Fasting blood sugar; 2HPP[#] - 2-hours post prandial; HR^Δ - Heart rate; SBP^Δ - Systolic blood pressure; DBP^Δ - Diastolic blood pressure; LVMl[†] - Left ventricular mass index

Table 2. Clinical and exercise treadmill test profiles of the subjects according to heart rate recovery

Variables	Delayed HRR	Normal HRR	p value
Age (years)	45.07±8.41	49.42±7.93	0.08
BMI (kg ⁻²)	24.24±2.96	24.71±3.55	0.65
FBS ^{**} (mmol/L)	10.34±3.52	8.82±1.73	0.11
2HPP [#] (mmol/L)	15.08±1.65	12.09±2.70	0.02
HR ^Δ (/min)	99.50±17.97	88.26±10.98	0.004
SBP ^Δ (mmHg)	116.43±5.15	116.75±6.59	0.86
DBP ^Δ (mmHg)	74.86±4.62	71.74±4.88	0.04
Pulse pressure (mmHg)	41.57±4.16	45.02±7.96	0.12
LVMl [†] (gm ⁻²)	89.36±17.49	84.24±15.06	0.28
Increased LVMl (%)	14.3	45.1	0.06
Peak SBP (mmHg)	195.00±10.18	203.96±12.77	0.07
Peak DBP (mmHg)	92.14±4.23	94.53±8.45	0.31
Peak HR (/min)	171.07±10.19	162.89±12.77	0.03
HR reserve	95.41±17.66	91.26±17.68	0.44
Recovery time	5.53±1.40	5.67±2.38	0.84

BMI - Body mass index; FBS^{**} - Fasting blood sugar; 2HPP[#] - 2-hours post prandial; HR^Δ - Heart rate; SBP^Δ - Systolic blood pressure; DBP^Δ - Diastolic blood pressure; LVMl[†] - Left ventricular mass index

Table 2 shows the clinical profile of subjects with delayed heart rate recovery compared with those with normal recovery. Subjects with abnormal or delayed HRR had significantly higher 2-hours post prandial plasma glucose, higher resting and peak heart rate as well as higher diastolic blood pressure.

3.3 Exaggerated SBP and HRR

HRR was significantly lower in subjects with ESBP response (23.00 ± 12.18 beats/minute) compared with those who had normal SBP

response (38.55± 22.69beats/minute); $P = 0.001$. Recovery time following exercise was also longer in the ESBP response group (Table 1). As shown in Fig. 1, the presence of abnormal HRR was 30.6% in subjects with ESBP response compared with 9.7% in subjects with normal BP response ($\chi^2 = 4.39$, $P = 0.036$).

4. DISCUSSION

The main finding of the present study was that HRR was lower in normotensive diabetics with ESBP and impaired HRR was more prevalent in

the same population of subjects compared with normotensive diabetics without ESBP. Other important findings were that the correlates of HRR in normotensive diabetics with ESBP were positively related to subject's fasting plasma glucose, body mass index, and pulse pressure; and negatively related to subject's resting heart rate and diastolic blood pressure. These findings suggest that ESBP and delayed HRR following treadmill maximal exercise response to exercise, two established prognostic markers, may reflect the same pathology via a reduction in vagal tone [10] or an exaggerated sympathetic activation [11]; a state of autonomic imbalance seen in some T2DM subjects.

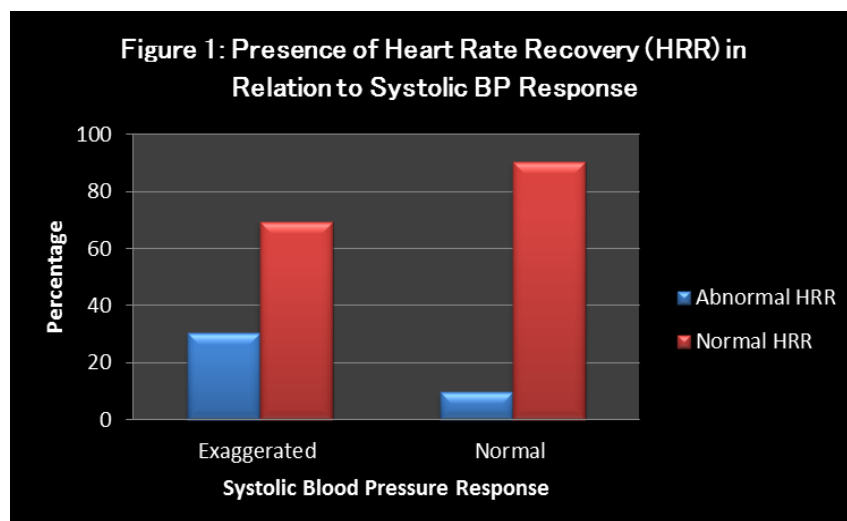
The link between ESBP and delayed HRR in normotensive diabetics is probably related to impaired regulation of the autonomic nervous system function. The immediate post-exercise period is associated with sympathetic tone withdrawal and a rebound vagal tone increase. Autonomic control and vaso-reactivity abnormalities during exercise could extend into the early recovery. Consequently, an ESBP response to exercise could be followed by a delayed HRR.

Several studies among Caucasians showed that the presence of ESBP response to exercise in normotensive diabetics was high. Karavelioglu et al. [13] reported a rate of 58% compared to 6% in non diabetic healthy individuals. Scott et al [17] showed that up to half of diabetic patients with normal blood pressure at rest have ESBP response to exercise. In the present study, we found ESBP response to exercise in our normotensive diabetic subjects to be 53.7%;

finding which is comparable with previous studies done among Caucasians. Ordinarily, reports have suggested that Blacks are more affected by diabetes associated with hypertension than whites and possibly related to lower socio-economic status [18,19].

In this study done among Blacks in Nigeria, the percentage of abnormal HRR was higher in subjects with ESBP (30.6 % vs 9.7 %, $P = 0.036$). This is in addition to the fact that subjects with ESBP response had significantly lower HRR compared with subjects with normal SBP response. These findings are similar to the findings of Dogan et al. [20] in their study in Turkey where the percentage of abnormal HRR in normotensive diabetic subjects with ESBP was 29% compared with those without ESBP which was 13%.

We observed in this study that more females had ESBP compared with males (58.3% vs 41.7%, $P = 0.003$). Similarly, we had earlier reported that even though there was no significant gender difference in chronotropic response to exercise in normotensive diabetics, more females had abnormal HRR compared with males [21]. It is known that many factors, including female gender, are associated with a reduction in exercise capacity and that the differences in exercise capacity between men and women have largely been attributed to non-modifiable differences in cardiac output and skeletal muscle mass [22,23]. However, other exercise variables such as HRR and ESBP response may be important additional factors in normotensive diabetics.



The cardiovascular prognostic implications of HRR and ESBP response to exercise in diabetes [5,6,24] are well documented. The roles of endothelial dysfunction in the development of exaggerated SBP response and HRR have been documented [25,26] as well. Endothelial function has been reported to be suppressed by increased sympathetic tone [26,27] as opposed to decrease in parasympathetic drive [28]. Heightened sympathetic nervous system activity and suppressed parasympathetic nervous system activity impair the ability of the autonomic nervous system to regulate the cardiovascular system. The link between delayed HRR and ESBP response to exercise and cardiovascular disease in normotensive diabetes is therefore speculated to be endothelial dysfunction, which is frequently seen in diabetes.

A major limitation of this study was the small sample size and non-measurement of glycated hemoglobin of the patients to assess glycemic control over a longer period of time.

5. CONCLUSION

ESBP response to exercise is present in more than half of normotensive diabetics and about a third of those patients with abnormal SBP response have delayed HRR. Imbalance in the autonomic nervous system, probably heightened sympathetic nervous system, may be responsible for these pathologies.

6. RECOMMENDATION

Studies involving larger study population be conducted in this environment to be able to make more general conclusion. Studies comparing Black and White normotensive T2DM are also suggested to determine if there are racial differences.

CONSENT

All authors declare that 'written informed consent was obtained from all the patients (or other approved parties) for publication of this article'.

ETHICAL APPROVAL

All authors hereby declare that the study protocol have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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