Original Article

Heart rate and blood pressure response to exercise and recovery in subclinical hypothyroid patients

Sunita, Aarti Sood Mahajan, AK Jain, NP Singh[1], TK Mishra[2]

Departments of Physiology, [2]Biochemistry, Maulana Azad Medical College [1]Department of Medicine, Lok Nayak and Pushpanjali Hospital, New Delhi, India

Abstract

Background: Exercise response of asymptomatic subclinical hypothyroid patients may aid in early diagnosis of cardiovascular morbidity. **Aim:** To study and compare the heart rate and blood pressure changes during exercise and recovery in subclinical hypothyroid patients and euthyroid controls. **Materials and Methods:** For the study, 30 each cases (mean age of 40 ± 7 years) of subclinical hypothyroidism and healthy controls underwent exercise as per Bruce protocol. Heart rate (HR) and blood pressure (BP) changes were compared every minute (min) till 3 min of stage II exercise, continued till maximum heart rate and thereafter on recovery, for 5 min after stoppage of exercise. **Results:** Both groups had normal HR and BP at rest, heart rate and BP increased with exercise and remained high even after 5 min of recovery from exercise. The increase in systolic blood pressure (SBP) with exercise was less in patients at the stage of exercise where maximum HR was achieved and up to 1 min of recovery. SBP at 5 min of recovery was higher in patients ($P = 0.018$). Diastolic blood pressure (DBP) increased with exercise and changes were similar in both groups during exercise and recovery. HR was higher in patients at 1 min of exercise. Changes in HR from 1 min of recovery to 2-5 min of recovery were significant in both groups. **Conclusion:** The present pilot study highlights that many parameters of HR and SBP during exercise and recovery in asymptomatic subclinical hypothyroid patients may differ from euthyroid, controls.

Key words: Blood pressure, exercise, heart rate, recovery, subclinical hypothyroidism

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Introduction

Subclinical hypothyroidism is the term used to describe patients with normal free thyroxine (T_4) and free triiodothyronin (T_3) and thyroid stimulating hormone (TSH) levels of more than 5 mIU/L, with generally no obvious symptoms of hypothyroidism.[1] There may be alterations in both myocardial function and changes in lipoprotein profile which results in increased risk of atherosclerosis, coronary heart disease, and myocardial infarction.[2,3] In asymptomatic patients, cardiac structure and function may remain normal at rest, but moderate to severe exercise may bring out hidden abnormalities.[4] These include reduced exercise stroke volume, reduced left ventricular ejection fraction, mild prolongation of pre ejection period, impaired exercise tolerance, lower maximum power output and maximal Oxygen consumption (VO_2), and higher heart rates with increasing workload.[5-7]

In a recent study, assessing cardiopulmonary parameters at fifth min of submaximal exercise in subclinical hypothyroid patients on levothyroxine treatment, it has been shown that baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP) remain unchanged but heart rate (HR) decreased indicating improvement in exercise performance.[8] Therefore, it is important to do a complete evaluation of exercise and recovery and not only baseline and peak parameters. This would increase the chances of bringing out hidden abnormalities that would have been missed otherwise. Thus this pilot study was done to evaluate and compare the HR and blood pressure (BP)

Address for correspondence: Dr. Aarti Sood Mahajan, Department of Physiology, Maulana Azad Medical College, New Delhi, India.
E-mail: aartis_mahajan@yahoo.co.in

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changes during exercise and up to 5 min of recovery between subclinical hypothyroid patients and euthyroid controls.

Materials and Methods

For the study, 30 patients, of either sex, 30-50 years of age were recruited from the medicine outpatient department. They had presented with non specific clinical features, some with clinical features of tiredness, decreased interest, and constipation. On investigation, those with biochemical profile (TSH more than 5 mIU/L, normal free T_3 and T_4) suggesting subclinical hypothyroidism were selected. Patients with overt hypothyroidism, hypertension, ischemic or valvular heart disease, arrhythmia, previous vascular surgery, heart failure, respiratory disease, pulmonary hypertension, hepatic or renal dysfunction, diabetes mellitus, significant neurological or psychological disease, malignancy and those receiving medications such as lithium carbonate, iodine and iodide containing drugs and smokers were excluded. The control group comprised 30 healthy individuals of same age and either sex, with normal T_3, T_4, and TSH, selected either from staff of hospital or relatives of patients. None of the subjects were undergoing any form of regular exercise training.

A complete pre exercise structured interview helped to collect medical history, physical examination and BP evaluation on two different occasions, electrocardiogram, were recorded for all participants who were then regularly followed up in the thyroid clinic. TSH was estimated by I^{125} gamma coat hTSH immunoradiometric assay, a 2 site "sandwich" assay, Diasorin USA. This had a normal reference range between 0.4 mIU/L and 3.1 mIU/L and a sensitivity of 0.013 mIU/L. The intraassay coefficient of variation (CV) of 1.0 mIU/L and 8.5 mIU/L were 3.2% and 3.1%, respectively. The interassay CV at 1 mIU/L and 9 mIU/L were 5.7% and 4.0%, respectively. The study protocol was approved by the institutional ethical committee and informed written consent was obtained from all participants prior to study.

Exercise testing

Prerequisite of testing

All subjects were instructed to refrain from any food (3 hours) and beverage (24 hours), and avoid physical exertion (48 hours) preceding the exercise test.[9,10] The test was conducted at 0900 hours in an air conditioned room with the subject wearing light weight clothes and comfortable shoes. The time was kept consistent to minimize the effect of circadian rhythm and the test was monitored by the same investigator to reduce inter rater variability and bias. An initial three minute warm up time was given to all participants for familiarization with the equipment and technique.

Exercise protocol

All the subjects underwent exercise treadmill test in the hospital lab using X–SCRIBE stress testing system (USA, 1993) according to Bruce protocol.[11] It was modified and a warm up period for 3 min was included. Predicted peak heart rate was calculated as 220-age. The protocol included a graded exercise pattern on a treadmill which started at a speed of 2.7 km/hr with 10% grade, increased after 3 min to second stage at 4.02 km/hr with 12% grade. This level is comparable to moderate submaximal exercise. HR and BP (SBP and DBP, with sphygmomanometer) were recorded at 1 min intervals till stage II of Bruce protocol. Participants were, however, allowed to continue exercise till the maximum HR was achieved but were instructed to stop exercise if they experienced any symptoms related to angina, light headedness, confusion, fatigue or if there were signs of cyanosis, significant fall in SBP of 10 mmHg, excessive rise in SBP >260 mmHg, DBP >115 mmHg, failure of HR to increase, and change in heart rhythm or failure of testing equipment.[12] During post exercise recovery phase, HR and BP were recorded for each min for a period of 5 min. Chronotropic response (CR) was calculated as [peak HR–resting HR/(220-age) -resting HR]; a value of <0.80 was considered as chronotropic incompetence. Heart rate recovery (HRR) was taken as the difference between maximum HR and the HR at specified time period after recovery.[13,14]

Statistical analysis

All data are expressed as mean ± standard deviation (SD). The analysis was performed using Statistical Package for Social Sciences (SPSS) (version 14.0, SPSS Inc, Chicago, IL). The Chi-square test was used to compare male/female ratio of subclinical hypothyroid patients and euthyroid controls. Statistical significance was accepted at $P < 0.05$ between paired and unpaired intragroup and intergroup analysis, respectively. Levene's test was carried out to test homogeneity of the variance. Comparison among control and cases were performed by two tailed student's *t*-test. The Mann Whitney test for two tailed significance was carried out for percentage (%) change in heart rate recovery. In addition, Wilcoxan signed rank test was done to assess difference in HR from 1 min of recovery to 2–5 min of recovery in both groups.

Results

The mean and standard deviation of patients age was 40. 43 ± 7.82 and it was similar to controls whose age was 41.13 ± 6.06, ($P = 0.700$). All were nonsmokers and had a sedentary lifestyle. Ninety percent of patients and 70% of controls were females and in the reproductive age group. The TSH of patients was 7.16 ± 1.23, significantly higher than controls, whose value was 3.12 ± 1.06, ($P = 0.000$). None of

Table 1: Exercise stress test parameters of the study groups

Parameters	Subclinical hypothyroid (*n*=30)	Euthyroid controls (*n*=30)	*P* value
Baseline HR (beats/min)	83.30±8.15	84.37±5.95	0.565
Baseline SBP (mmHg)	129.93±14.64	125±6.53	0.097
Baseline DBP (mmHg)	80.80±8.58	80.60±4.04	0.908
Chronotropic incompetence	0.85±0.33	0.94±0.07	0.164
Max heart rate achieved at the end of exercise (beats/min)	174.0±16.53	174.33±5.87	0.92
SBP (mmHg) corresponding to max heart rate achieved at the end of exercise	170.67±17.36	190.00±72.4	0.000
DBP (mmHg) corresponding to max heart rate achieved at the end of exercise	91.60±8.04	88.87±3.04	0.087

All results are mean±standard deviation, *P*<0.05 is significant, SBP, DBP, and HR refer to systolic blood pressure, diastolic blood pressure and heart rate, respectively. Max indicates maximum; HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

the patients were being treated with thyroxine The baseline HR, BP, and exercise stress test parameters of the two groups are mentioned in Table 1.

SBP changes with exercise and recovery (subclinical hypothyroid cases vs. controls)

In both groups, a significant increase in SBP compared to baseline values was observed during exercise and recovery ($P < 0.001$) [Figure 1].

Comparison between groups showed that SBP corresponding to maximum HR achieved was higher in controls [Table 1]. Also, SBP achieved at the end of 1-6 min of exercise and 1 min of recovery was more in the control group ($P = 0.041, 0.002$ for 1 and 2 min of exercise and $P = 0.000$ for 3-6 min of exercise and 1 min of recovery). However, SBP at 5 min of recovery was higher in subclinical hypothyroid patient ($P = 0.018$) [Figure 1].

When the ratio of SBP (peak to resting) and (peak to 1-5 min of recovery) were compared; they were significantly different in the two groups ($P < 0.001$ for all except peak to 1 min of recovery where $P = 0.010$). Ratio of SBP (peak to 3 min recovery) was 0.88 in patients and 0.79 in controls.

SBP ratios at recovery were also different in the two groups. SBP ratios (1 min of recovery to 3 min of recovery, $P = 0.000$), (2 min recovery with resting, 4, 5 min recovery; $P = 0.001, 0.000, 0.000$, respectively) were different in two groups. Ratio of SBP (2-3 min recovery) was similar in two groups. Ratios of SBP (3 min recovery and 4 min recovery with 5 min recovery) were significantly different in two groups ($P = 0.002, 0.005$, respectively).

DBP changes with exercise and recovery

In both groups, a significant increase in DBP compared to baseline values was observed during exercise and

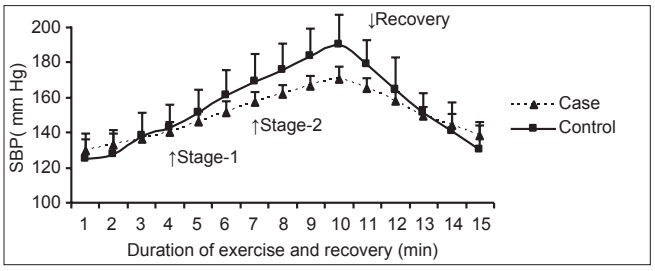

Figure 1: Changes in Systolic Blood Pressure with duration of exercise and recovery period (5 min post exercise) in subclinical hypothyroid patients (cases) and euthyroid controls

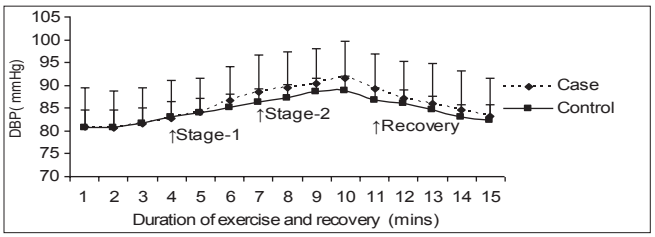

Figure 2: Changes in Diastolic Blood Pressure with duration of exercise and recovery period (5 min post exercise) in subclinical hypothyroid patients (cases) and euthyroid controls

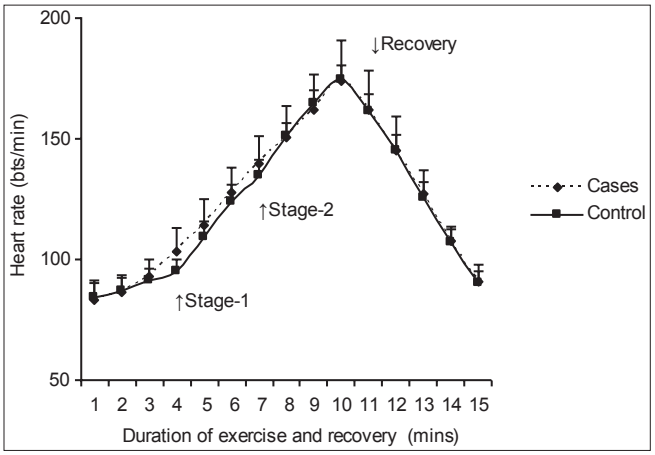

Figure 3: Changes in Heart Rate with duration of exercise and recovery period (5 min post exercise) in subclinical hypothyroid patients (cases) and euthyroid controls

recovery ($P = 0.000$ for all except $P = 0.004$, $P = 0.021$ for 4 and 5 min of recovery in subclinical hypothyroid cases, respectively) [Figure 2]. No significant differences in DBP response between the two groups were found.

Heart rate changes with exercise

In both groups, a significant increase in HR compared to baseline values was observed during exercise and recovery ($P = 0.000$ for all) [Figure 3]. Even at 5 mins of recovery, HR was higher than baseline value.

Comparison between the two groups showed that HR of subclinical hypothyroid patients was higher than controls at 1 min of stage 1 exercise ($P = 0.034$) [Figure 3]. All other

comparisons of HR were not significantly different between cases and control. These include HR found from 2-5 min of exercise and up to 5 min of recovery, maximum HR achieved at the end of exercise [Table 1], HRR (peak to 1-5 min of recovery) and percentage change in HRR (1 min recovery to 2-5 min of recovery). However, both groups showed significant reduction in HR from 1 min of recovery to 2-5 min of recovery (P = 0.000 for all).

Chronotropic response was similar in the two groups [Table 1].

Discussion

This pilot study provided a comprehensive comparison of exercise and recovery pattern between subclinical hypothyroid patients and euthyroid controls. As many parameters of HR and BP response to exercise and recovery for a period of 5 min were evaluated and compared, our study was different from others which have evaluated exercise performance in subclinical hypothyroid patients. There was a blunted increase in SBP during exercise and a delayed SBP decline during recovery among patients. Mean SBP of patients were less compared to controls from 1 min of stage 1 exercise till 1 min of recovery. However, at 5 min of recovery, the SBP of patients was more. Akcakoyun *et al*., found no difference in SBP at rest or during exercise between subclinical hypothyroid patients and controls and Mainenti *et al.,* reported a lower increase in SBP from resting to peak in patients and no difference in SBP recovery between patients and controls in two studies.[10,13,15]

McHam *et al.,* considered the ratio of SBP at 3 min of recovery to 1 min of recovery and ratio of SBP at 3 min of recovery to peak exercise to assess the decline in SBP during recovery. The 3:1 min ratio during recovery reflecting a delayed decline of SBP was considered a predictor of coronary artery disease (CAD).[16] In our present study, this 3:1 min ratio is significantly higher in patients. The present study also shows ratio of SBP from peak to resting and peak to 1-5 min of recovery were significantly lower in patients. This is similar to finding of Mainenti *et al*.[15] Although, the peak to 3 min SBP was not significantly different in the two groups studied by McHam *et al*.,[16] we found significant difference in SBP ratio from peak to 1-5 min of recovery. It has been reported that if this ratio is greater than 0.90, it has a diagnostic accuracy of approximately 75% for detection of CAD.[17] Our patients had a ratio less than 0.9 but the ratio was higher compared to the ratio in control group. Amon *et al.,* reported that a delay in decline of SBP after exercise was more accurate than ST segment depression for the diagnosis of CAD.[18] Therefore, these parameters studied are useful for early diagnosis of CAD in subclinical hypothyroid patients.

The mechanism of delayed decrease in SBP after exercise may be a combination of various factors. In patients of CAD, during exercise, there is left ventricular asynergy, increase catecholamine release, and peripheral vasoconstriction compensatory to ischemia induced left ventricular systolic dysfunction. After exercise is stopped, all this could persist a few minutes into recovery. This may explain why patients with severe coronary disease have higher BP during early recovery than those without disease.[16] The elevated SBP after exercise may reflect upon a person's physical fitness, aerobic capacity, over activity of sympathetic nervous system and attenuated vagal reactivation.[19] Autonomic dysfunction and vasoreactivity abnormality have also been suggested by Singh *et al*.[20]

No significant differences in DBP increase with exercise or decrease during recovery was found between two groups. This is similar to finding of Akcakoyun *et al*.[13] However, Mainenti *et al.,* reported a higher pre exercise DBP in patients and a diastolic dysfunction during exercise with a slower recovery between 1 min and 3 min.[15]

In this study, for both groups the HR increased during exercise and remained so, even after 5 min of recovery. This has also been observed earlier in a group of 485 healthy individuals.[14] Also, in comparison to controls, our patients had a higher HR at 1 min of stage 1 exercise, while no difference was observed in recovery pattern. HRR from peak to 1-5 min of recovery and percentage change in HRR was similar in both groups. The increased heart rate in the first minute of exercise has previously been suggested as a novel autonomic marker that helps in accurate diagnosis of high risk CAD patients.[21] In a study of 23 subclinical hypothyroid patients, Caraccio *et al.,* found that with increasing workload, patients achieved a higher HR. In their opinion, a reduced cellular oxygen extraction, with a possible mitochondrial defect may contribute to impaired oxygen use in subclinical hypothyroid patients.[7] In another study, there was no significant change in HR at rest or during exercise between groups, whereas HRR was significantly lower during exercise testing in subclinical hypothyroid patients compared to control and chronotropic incompetence was found in patients.[13] This study was different from ours because we found significant difference at 1 min of exercise between patients and control, there was no chronotropic incompetence in our patients and we studied HRR till 5 min of recovery from exercise. Similarly, Mainenti *et al.,* reported the lower values of HR for patients at the end of test.[15] It has been suggested that a delayed decrease in HR during 1 and 2 min recovery of graded exercise, may be a reflection of decreased vagal activity and is a powerful predictor of overall mortality.[22,23]

Conclusion

In conclusion, there are variations in HR and BP response during exercise and recovery between subclinical hypothyroid patients and controls. HR at 1 min of exercise is higher in patients, there is a lesser increase in SBP during exercise and delayed decline in SBP during recovery. Variations exist between ratios of various parameters during exercise and recovery. More studies are required to identify the best indicator. Thus, exercise testing, which includes studying both HR and BP responses during exercise and up to 5 min of recovery, can help to bring out latent abnormalities, which may identify apparently asymptomatic subclinical hypothyroid patients who may be at risk of developing CAD.

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