Original Article

Moderate intensity exercise improves heart rate variability in obese adults with type 2 diabetes

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A B S T R A C T

Aim: The aim of this study was to determine the effect of moderate aerobic exercise on heart rate variability (HRV) in obese adults with type 2 diabetes.
Methods: Forty-one obese adults with type 2 diabetes participated in this study. Anthropometric and metabolic parameters were measured, and resting electrocardiogram (ECG) for the HRV analysis at spontaneous respiration was recorded for 5 min in supine position before and after six months of supervised aerobic training given thrice-a-week.
Results: The mean age, body mass index (BMI), and duration of diabetes of the study population were 44.1 ± 4.5 years, 30.94 ± 1.36 kg/m2, and 16.3 ± 2.7 years, respectively. In time domain variables, standard deviation of all RR intervals (SDNN), the square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD) and percentage of consecutive RR intervals that differ by more than 50 ms (pNN50) were significantly increased after exercise. In frequency domain variables, high frequency (HF) (ms2) and HF (nu) were significantly increased while low frequency (LF) (ms2) and LF/HF ratio were significantly decreased after exercise. But LF (nu) was unaffected after exercise.
Conclusion: This study suggests that thrice-a-week moderate intensity aerobic exercise for six months improves cardiac rhythm regulation as measured by HRV in obese adults with type 2 diabetes

1. Introduction

Several populations based studies show that regular physical activity is an important component of a healthy lifestyle and lack of activity is a predictor of cardiovascular mortality.[1,2] Physical inactivity is closely related to cardiovascular disease and a widening variety of other chronic diseases, including type 2 diabetes, obesity and hypertension.[3] Many studies have suggested beneficial effects of regular exercise in preventing sudden cardiac death in healthy individuals and in patients with cardiovascular diseases.[4,5]

It is commonly perceived that a regular heart beat with sinus arrhythmia is a sign of healthy heart. Thus, the rhythm of a healthy heart is characterized by significant beat to beat variability.[6] This heart rate variability (HRV) has been recognized as a powerful tool in the investigation of autonomic modulation of heart. Patients with type 2 diabetes exhibit altered autonomic modulation of heart as assessed by HRV.[7] Decreased HRV among patients with diabetes has been found to be predictive of cardiovascular morbidity and mortality.[8,9] Obesity, a key risk factor for the development of type 2 diabetes, is associated with dysregulation of autonomic nervous function.[10] It has been proposed that autonomic dysregulation is an important mediator in the development of obesity-associated diseases and insulin resistance although the nature of the link between adiposity and insulin sensitivity is still unclear.[11,12]

Exercise therapy has been shown to improve autonomic nervous system modulation of HRV in healthy individuals.[13–15] Therefore, exercise training may improve cardiac autonomic regulation in a variety of clinical populations including obese adults with type 2 diabetes. Thus, the main aim of this study was to determine the effect of thrice-a-week, six months, moderate aerobic exercise on cardiac autonomic function as measured by HRV in obese adults with type 2 diabetes.

2. Materials and methods

2.1. Subjects

Forty-one obese male adults with type 2 diabetes volunteered to participate in a supervised thrice-a-week aerobic training of

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moderate intensity for six months. The exclusion criteria were overt cardiovascular disease, diabetic complications (e.g. nephropathy, retinopathy), chronic heart failure, hypertension, arrhythmias, known neuropathy of any other etiology, comorbid conditions (e.g. cancer, immunodeficiency, autoimmune diseases) and current smoking. The subjects with Ewing Score ≥3 and vibration perception threshold ≥6 V were also excluded from the study. The ethical clearance was obtained from the Ethics Committee of the College. Informed consent was obtained from all participants before commencement.

2.2. Clinical examination

In the personal interview with the subjects, detailed history was obtained with special reference to age, duration, symptoms of neuropathy, diabetes related complications and medication. All the participants were subjected to clinical examination.

Each participant underwent the measurement of his weight and height recorded while wearing light indoor clothes but no shoes. Body mass index (BMI) was calculated as weight in kilograms/ height in meters squared as a measure of overall adiposity whereas waist circumference (midway between the lower rib margin and the top of the iliac crest) was considered a measure of central or abdominal adiposity.[16] Blood pressure was measured using standard protocol. In addition, they underwent a detailed neurological examination. Non-invasive Ewing battery tests: Valsalva maneuver, Heart rate response to standing, Heart rate response to deep breathing, Blood pressure response to standing, Blood pressure response to sustained handgrip were also performed for cardiac stress before undergoing an exercise program. Ewing scores were assigned as follows: 0 for a normal test, 0.5 for a borderline, and 1 for an abnormal value.[17] Peripheral somatic neuropathy was assessed by a biothesiometer (Genesis Medical System, India), measuring vibration perception threshold at toe, first metatarsal, third metatarsal, fifth metatarsal, instep, and heel surfaces of each foot.[18]

On the days before testing, all the participants were medication free and stable in terms of cardiopulmonary function. Possible diurnal variation was minimized by carrying out all tests in the same sequence between 09:00 and 11:00 A.M.

2.3. Training program

The participants were enrolled in a six-month program of aerobic exercise. Under the supervision by trained personnel, they performed thrice-a-week sessions of physical activity. In order to produce the desired metabolic effects, each exercise session lasted 50 min; 10 min of warm-up, 30 min of activity (brisk walking, light running), and 10 min of cool-down. Considering the linear relationship between heart rate and %VO$_2$ reserve, exercise intensity was set between 50% to 70% of maximum heart rate, which was calculated by the following formula: $[(220 - age - resting\ heart\ rate) \times \%$ of maximum heart rate + resting heart rate].[19]

2.4. HRV measurement

The ECG signals for HRV were recorded using ECG machine (Maestros Magic R Series, India) after a supine rest of 15 min. The resting ECG at spontaneous respiration was recorded for five min in supine position at chart speed 100 mm/s. From ECG, RR intervals were measured manually with a ruler. Then these RR intervals were saved as ASCII file. This format was readable by software 'HRV analysis software 2.1'. This HRV analysis software, which calculates the time domain results, frequency domain results, and nonlinear

results was developed by Department of Applied Physics, University of Eastern Finland, Kuopio, Finland.

The time domain analysis of HRV consisted of the standard deviation of all RR intervals (SDNN); the square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD); and pNN50, which is the proportion of the total RR intervals that have differences of RR intervals greater than 50 milliseconds.[20]

The frequency-domain analysis of HRV consisted of power of high frequency (HF), (0.15–0.40 Hz); low frequency (LF), (0.04–0.15 Hz); and very low frequency (VLF), (below 0.04 Hz) power ranges.[20]

It has been speculated that analysis of HRV based on the methods of nonlinear dynamics might elicit valuable information for the physiological interpretation of HRV. One nonlinear method is Poincare plot. The Poincare plot is a scatterplot of the current RR interval plotted against the preceding RR interval. Using the method described by Brennan,[21] these plots were used to extract indexes, such as length (SD2) and width (SD1) of the long and short axes of Poincare plot images.

2.5. Biochemical measurements

Venous blood was drawn in the morning after an overnight fast immediately before (baseline) and at the end of the training program (after six months). Plasma glucose was measured by standard laboratory procedures (BS-380; Diagnova Enzokit, RFCL, India). Total cholesterol and triglycerides concentration were determined with fully enzymatic analyzer (BS-380; Diagnova Enzokit, RFCL, India). Similarly, serum HDL-cholesterol level was estimated by phosphotungstate precipitation method and serum LDL-cholesterol was calculated by the Friedewald equation. HbA$_{1c}$ was measured by ion exchange affinity chromatography (Kamineni life sciences, Hyderabad, India).

2.6. Statistical analysis

Different anthropometric, cardiorespiratory and biochemical variables were compared before and after exercise using paired samples t-test and data are presented as mean ± standard deviation. However, non-parametric Wilcoxon signed-rank test was applied for comparisons of the HRV variables and the results are presented as median (interquartile range). The Pearson correlation coefficient was used to assess correlation between the HRV measures and the obesity indices (BMI and waist circumference) as well as between the obesity indices and the biochemical characteristics. A p value of <0.05 was considered statistically significant. Data were analyzed with statistical software IBM SPSS Statistics 21.

3. Results

3.1. Subject characteristics

The clinical characteristics of participants are shown in Table 1. All these variables were significantly decreased after exercise.

Table 2 shows biochemical characteristics of participants. All these variables were significantly decreased after exercise, except high-density lipoproteins which was significantly increased after exercise.

3.2. Heart rate variability measures

In the time domain variables, SDNN, RMSSD and pNN50 were significantly increased after exercise. The variables analyzed in frequency domain measures included power of LF and HF in ms^2

Table 1
Clinical characteristics of participants before and after 6 months of exercise (n = 41).

Variables	Before exercise	After exercise	p value
Age (years)	44.2 ± 4.5		
Diabetes duration (years)	16.4 ± 2.7		
Height (cm)	169.33 ± 4.3		
Weight (kg)	87.80 ± 4.22	84.90 ± 4.58	0.001
BMI (kg/m^2)	32.94 ± 1.37	29.95 ± 1.23	0.003
WC (cm)	97.66 ± 2.2	94.4 ± 2.8	0.001
SBP (mmHg)	122.3 ± 6.2	118.44 ± 3.2	0.002
DBP (mmHg)	84.84 ± 3	79.84 ± 3.2	0.001
Pulse rate	75.17 ± 8.06	70.93 ± 6.1	0.003
Respiratory rate	15.67 ± 5.12	13.36 ± 7.5	0.001

The $p < 0.05$ was considered statistically significant.
BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure. Results are expressed as mean ± SD.

and their normalized units (nu), and ratio of LF to HF (LF/HF). The HF (ms^2) and HF (nu) were significantly increased after exercise, whereas LF (nu) was unaffected. But LF (ms^2) and LF/HF ratio were significantly decreased after exercise. In Poincare plot SD1 and SD2 were significantly increased while ratio of SD2 to SD1 (SD2/SD1) were significantly decreased after exercise (Table 3).

3.3. Indices of obesity and heart rate variability measures

The waist circumference negatively correlated with SDNN ($r = -0.52$, $p < 0.001$), RMSSD ($r = -0.38$, $p < 0.001$) and HF (nu) ($r = -0.31$, $p < 0.013$) while positively correlated with LF (nu) ($r = 0.46$, $p < 0.016$) and LF/HF ($r = 0.44$, $p < 0.001$) before exercise (Table 4). That is, the larger the waist circumference, the lower vagal modulation and higher sympathovagal balance the participants had. It is noteworthy that BMI correlated with none of the HRV measures before exercise. All correlations between indices of obesity and HRV measures were unaffected after exercise.

3.4. Heart rate variability and biochemical characteristics

RMSSD negatively correlated with fasting glucose ($r = -0.70$, $p < 0.001$), HbA$_{1c}$ ($r = -0.55$, $p < 0.001$), total cholesterol ($r = -0.47$, $p < 0.002$), LDL ($r = -0.67$, $p < 0.001$) and triglycerides ($r = -0.68$, $p < 0.001$). HF (nu) negatively correlated with fasting glucose ($r = -0.46$, $p < 0.001$), HbA$_{1c}$ ($r = -0.56$, $p < 0.001$), total cholesterol ($r = -0.77$, $p < 0.001$), LDL ($r = -0.59$, $p < 0.001$) and triglycerides ($r = -0.48$, $p < 0.001$) (Table 5). These suggest that elevated levels of fasting glucose, HbA$_{1c}$, total cholesterol, LDL and triglycerides are associated with reduction in HRV before exercise in participants. No significant relation was observed between other variables of HRV and biochemical characteristics in participants before and after exercise.

Table 2
Biochemical characteristics of participants before and after 6 months of exercise (n = 41).

Variables	Before exercise	After exercise	p value
Fasting glucose (mg/dl)	164.7 ± 8.08	113.4 ± 8.9	0.001
HbA$_{1c}$ (%)	10.44 ± 2.24	8.45 ± 1.32	0.001
Total cholesterol (mg/dl)	251.4 ± 16.49	166 ± 18.4	0.002
LDL (mg/dl)	160.3 ± 5.83	120.3 ± 6.08	0.001
HDL (mg/dl)	43.8 ± 7	81.1 ± 6.2	0.001
Triglycerides (mg/dl)	175.6 ± 14.65	89.8 ± 13.42	0.001

The $p < 0.05$ was considered statistically significant.
HbA$_{1c}$, glycated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein. Results are expressed as mean ± SD.

Table 3
HRV parameters of participants before and after 6 months of exercise (n = 41).

Variables	Before exercise	After exercise	p value
SDNN (ms)	22 (12.5–33.25)	36 (30.75–40)	0.001
RMSSD (ms)	22.5 (11.65–37)	32.5 (24.4–40.9)	0.001
pNN50 (%)	3.5 (0.15–16.25)	13 (3.62–22.5)	0.001
LF (ms^2)	155 (114–262.75)	48 (18.25–116)	0.001
LF (nu)	47.4 (37.68–69.45)	38.65 (29.75–57.25)	NS
HF (ms^2)	57.5 (8.5–209.75)	175.5 (106.75–265.75)	0.002
HF (nu)	50.7 (30.38–60.48)	61.35 (42.75–70.25)	0.004
LF/HF (%)	0.97 (0.65–2.29)	0.63 (0.42–1.35)	0.001
SD1 (ms)	16 (10–23)	31 (19–37)	0.001
SD2 (ms)	34 (23–48)	41 (27–70)	0.001
SD2/SD1	2.04 (1.46–3.06)	1.58 (0.91–2.64)	0.001

The $p < 0.05$ was considered statistically significant.
SDNN, standard deviation of all RR intervals; RMSSD, the square root of the mean of the sum of the squares of differences between adjacent RR intervals; pNN50, percentage of consecutive RR intervals that differ by more than 50 ms; LF, low frequency; HF, high frequency; nu, normalized unit; SD1, standard deviation perpendicular to line of entity in Poincare plot; SD2, standard deviation along the line of entity in Poincare plot; NS, statistically non-significant. Results are expressed as median (interquartile range).

3.5. Indices of obesity and biochemical characteristics

The waist circumference positively correlated with total cholesterol ($r = 0.31$, $p < 0.013$) and LDL ($r = 0.21$, $p < 0.018$) before exercise while negatively correlated with HDL ($r = -0.28$, $p < 0.011$) after exercise (Table 6). No significant relation was observed between indices of obesity and other biochemical characteristics in participants before and after exercise.

4. Discussion

This study was designed to determine long term cardiovascular autonomic adaptation to moderate aerobic exercise program in obese adults with type 2 diabetes. The finding of the current study indicates predictable change in cardiac autonomic activity as measured by HRV, among obese adults with type 2 diabetes.

Cardiac autonomic neuropathy is a serious complication of type 2 diabetes, shown to influence both cardiovascular diseases and mortality in these patients[22,23]; and type 2 diabetes also reduces HRV, presumably reflecting a decrease in cardiac autonomic function.[7,18] Therefore, type 2 diabetes may attenuate or obviate the beneficial effects of exercise on HRV and other markers of cardiovascular health in those patients with this comorbidity. Surprisingly, HRV increased with exercise in obese adults with concomitant type 2 diabetes, indicating that exercise is producing beneficial effects on cardiovascular autonomic function.

In type 2 diabetes, the impairment of parasympathetic function with a relatively increase of sympathetic function causing an imbalance of the sympathetic/parasympathetic tone. Regular exercise modulates cardiac autonomic control by enhancing vagal tone and lessening sympathetic influence.[5] This shift toward greater vagal modulation may positively affect the prognosis of individuals with a variety of morbidities.[24] Several biological mechanisms have been proposed but the relative importance of these exercise-related mechanisms is still unknown.[4] They could possibly be related to subsequent improvements in body fat distribution, atherogenic lipoprotein profiles and blood pressure, as well as beneficial effects on muscular capillary density and autonomic nervous system balance.[25] In diabetes mellitus, physical activity has beneficial effects on both glucose metabolism and insulin sensitivity. These include increased sensitivity to insulin, decreased production of glucose by liver, large number of muscle cells that utilize more glucose than adipose tissue, and reduced obesity.[26]

Table 4
Correlations among indices of obesity and heart rate variability measures using Pearson correlation coefficient before 6 months of exercise.

Indices of obesity	Heart rate variability measures								
	SDNN	RMSSD	pNN50	LF	HF	LF/HF	SD1	SD2	SD2/SD1
WC	−0.52 0.001	−0.38 0.001	NS	0.46 0.016	−0.31 0.013	0.44 0.001	NS	NS	NS
BMI	NS	NS	NS	NS	NS	NS	NS	NS	NS

In each cells, the number described above is correlation coefficient, and the number below is *p* value of Pearson correlation coefficient. WC, waist circumference; BMI, body mass index; SDNN, standard deviation of all RR intervals; RMSSD, the square root of the mean of the sum of the squares of differences between adjacent RR intervals; pNN50, percentage of consecutive RR intervals that differ by more than 50 ms; LF, low frequency; HF, high frequency; SD1, standard deviation perpendicular to line of entity in Poincare plot; SD2, standard deviation along the line of entity in Poincare plot; NS, statistically non-significant.

Table 5
Correlation among heart rare variability measures and biochemical characteristics using Pearson correlation coefficient before 6 months of exercise.

Biochemical Characteristics	Heart rate variability measures								
	SDNN	RMSSD	pNN50	LF	HF	LF/HF	SD1	SD2	SD2/SD1
Fasting glucose	NS	−0.70 0.001	NS	NS	-0.46 0.001	NS	NS	NS	NS
HbA$_{1c}$	NS	−0.55 0.001	NS	NS	-0.56 0.001	NS	NS	NS	NS
Total cholesterol	NS	−0.47 0.002	NS	NS	-0.77 0.001	NS	NS	NS	NS
LDL	NS	−0.67 0.001	NS	NS	-0.59 0.001	NS	NS	NS	NS
HDL	NS	NS	NS	NS	NS	NS	NS	NS	NS
Triglycerides	NS	−0.68 0.001	NS	NS	-0.48 0.001	NS	NS	NS	NS

In each cells, the number described above is correlation coefficient, and the number below is *p* value of Pearson correlation coefficient. SDNN, standard deviation of all RR intervals; RMSSD, the square root of the mean of the sum of the squares of differences between adjacent RR intervals; pNN50, percentage of consecutive RR intervals that differ by more than 50 ms; LF, low frequency; HF, high frequency; SD1, standard deviation perpendicular to line of entity in Poincare plot; SD2, standard deviation along the line of entity in Poincare plot; HbA$_{1c}$, glycated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NS, statistically non-significant.

It has been shown that obesity is associated with impaired autonomic function both in healthy subjects[27] and patients with type 2 diabetes.[28] HRV is a validated and easily obtainable measurement of the influence of autonomic function on the heart and by itself associated with cardiovascular risk factors and mortality.[29] In the present study, RMSSD and pNN50, which reflects the vagal tone were statistically increased after exercise. The RMSSD and pNN50 also correlate highly with HF power, reflecting parasympathetic modulation.[30] Similarly, SDNN which reflects total variability and carries the strongest prognostic information in heart disease was also increased after exercise. Thus, the time domain analysis of HRV showed increased parasympathetic activity in obese subject with type 2 diabetes after exercise.

By using more specific information obtained from frequency domain measures concentrated around respiratory frequency, HF (ms^2) and HF (nu) were significantly increased after exercise; LF (ms^2) and LF/HF ratio were significantly decreased while LF (nu) was unaffected after exercise. The HF component of HRV is

Table 6
Correlation among indices of obesity and biochemical characteristics using Pearson correlation coefficient before 6 months of exercise.

Indices of obesity	Biochemical characteristics					
	Fasting glucose	HbA$_{1c}$	Total cholesterol	LDL	HDL	Triglycerides
WC	NS	NS	0.31 0.013	0.21 0.018	NS	NS
BMI	NS	NS	NS	NS	NS	NS

In each cells, the number described above is correlation coefficient, and the number below is *p* value of Pearson correlation coefficient. HbA$_{1c}$, glycated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NS, statistically non-significant.

considered to represent the vagal control of heart rate.[31–33] Some authors have suggested that the LF component is a quantitative marker of sympathetic modulation[34,35] and others that it is a marker of both sympathetic and vagal modulation.[36,37] The LF/HF ratio is considered to reflect sympathovagal balance, and acts as an indicator for the sympathetic nervous activity.[34,35] LF/HF ratio decreased after six months of exercise. It might be due to either decreased in LF (ms^2) or increased in HF (ms^2). In this study, an increased HF (ms^2) and a diminished LH (ms^2) were observed after six months of exercise. These changes indicate a shift of sympathovagal balance towards parasympathetic predominance and reduced sympathetic tone. The LF (nu) is also considered as a marker of sympathetic nervous function.[20] Thus, frequency domain analysis of HRV indicates that increased in vagal activity and decreased in sympathetic activity in obese subject with type 2 diabetes after exercise.

In Poincare plot measures, SD1 and SD2 were significantly increased after exercise. Analysis of the SD2/SD1 ratio provides information on the relationship between sympathetic and parasympathetic tone. The present study showed a lower ratio after exercise. A lower SD2/SD1 ratio may reflect a decrease in SD2, an increase in SD1, or both. An increase in SD1 means an increase in parasympathetic activity while an increase in SD2 means a decrease in sympathetic activity.[38–40] In the present study increase in SD1 was greater than in SD2, so a lower ratio implies both an increased vagal tone and decreased sympathetic influence in trained obese subjects.

The present study showed that central adiposity, measured by waist circumference, was associated with the higher sympathetic and lower vagal modulations before exercise but was not associated with either measure of HRV after exercise. Overall adiposity, measured by BMI, was not associated with either measure of HRV before and after the intervention period. Thus,

abdominal adiposity, as opposed to overall adiposity, could adversely affect cardiovascular autonomic function measured by HRV. BMI is universally accepted as the index of obesity. However, waist circumference, an index of abdominal obesity, is more closely related to the increased risk of type 2 diabetes and cardiovascular mortality than that of overall obesity.[41–43]

Fasting glucose, glycated hemoglobin (HbA_{1c}), total cholesterol, low-density lipoproteins and triglycerides which are surrogate markers of global vascular health, also decreased after exercise while high-density lipoproteins increased. These metabolic markers have previously been identified as independent markers of cardiovascular health.[44] Poor glycemic control leads to accelerated cardiovascular disease resulting in elevated morbidity and mortality. Moderately intense levels of aerobic training has been found to be effective at improving glycemic control in people with diabetes.[45] The improvements in glycemic control commonly result in reduction in diabetes medications.[46] While moderate intensity exercise has been effective in increasing HDL cholesterol, the intensity of aerobic exercise must be increased to reduce LDL cholesterol and triglycerides levels.[47] Most of the subjects in this study were farmers and they were also involved in other physical activities. That might be the reason why LDL cholesterol and triglycerides levels reduced although they did moderate exercise. Whereas low HDL levels are associated with cardiovascular mortality, moderate exercise results in reduction in the risk of atherosclerosis and coronary heart disease.[48] It has been reported that reductions in LDL cholesterol decreases the incidence of heart attacks and ischemic strokes.[49]

As the present study was limited by small sample size, further studies in a large number of obese adults with type 2 diabetes are needed to confirm that these beneficial effects observed in the biochemical and autonomic variables after the training period have favorable effects on the clinical outcome of the patients. In addition, this study was unable to confirm these beneficial effects were only because of exercise program because participants were also on medication during the program. Further study with control group is required to confirm the above statement. Since waist circumference, index of central obesity, is more pathophysiologically related to the imbalance in the autonomic nervous modulation, it is suggested that the waist circumference should be measured in clinical practice, in addition to the weight or BMI.

In conclusion, thrice-a-week, six-month, moderate, supervised aerobic training program in obese adults with type 2 diabetes who were clinically free of cardiovascular disease leads to significant improvements in cardiovascular autonomic function measured by HRV via increasing cardio-vagal tone and decreasing cardio-sympathetic tone. In addition, our findings also suggest that thrice-a-week moderate intensity aerobic exercise are safe and could serve as a potential adjunct therapy in the management of obese people with type 2 diabetes. Also, exercise and physical activity can be utilized to improve lipid profile.

Acknowledgment

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