

Relationship of Gender and Lipid Profile with Cardiac Parasympathetic Reactivity

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ABSTRACT

Background: Lower heart rate variability has been proven to be associated with a greater risk for developing hypertension among normotensive men, and hypertension is one of the major risk factor of coronary heart disease. Hormonal factors in premenopausal women may cause variance in heart rate variability and impact lipid profile. **Objectives:** The study was designed to evaluate the relationship of gender and lipid profile with cardiac parasympathetic reactivity. **Materials and Methods:** Sixty premenopausal and 60 postmenopausal women along with 60 young and 60 elderly, age and body mass index (BMI) matched men without any apparent illness were selected. Cardiac parasympathetic reactivity during Valsalva maneuver, deep breath test, and 30:15 R-R interval ratios were studied and lipid profile analyzed. **Results:** Lipid profile showed significant increase in values of total cholesterol, low density lipoprotein (LDL), triglyceride, and significant decrease in high density lipoprotein (HDL) values in younger males when compared with premenopausal females and no difference in these parameters were noticed when comparison was done between elderly males and females. Deep breath test and 30:15 R-R interval ratios showed significant decrease in values in younger males when compared with age matched premenopausal females. Total cholesterol, triglyceride, LDL were negatively correlated with parasympathetic function tests; whereas HDL was positively correlated with parasympathetic function tests. **Conclusion:** Sex hormone levels may alter the autonomic nervous system response and lipid metabolism and lipids play an important role in modulation of autonomic functions.

KEY WORDS: Parasympathetic reactivity, gender, lipid metabolism

INTRODUCTION

Autonomic nervous system balance can be assessed non-invasively by the use of heart rate variability (HRV). Reduced HRV is associated with a greater risk for developing coronary heart disease (CHD). Acute myocardial infarction (AMI) is accompanied by decreased HRV, which is due to reduced vagal or increased sympathetic outflow to the heart.^[1-3] Hormonal factors may be a cause of variance in HRV among males and females.^[4] Estrogen is known to be a vagotonic and sympatholytic hormone. A metabolite of progesterone is known to have sympatholytic activity.^[3-5]

Dyslipidemia may also cause autonomic dysfunction.^[2,3] Testosterone increases circulating levels of low density lipoprotein (LDL) cholesterol and decreases plasma high

density lipoprotein (HDL) cholesterol. Estrogens have a significant plasma cholesterol lowering action and they rapidly produce vasodilatation by increasing the local production of nitric oxide. These actions inhibit atherogenesis and contribute to the low incidence of AMI and other complications of atherosclerotic vascular disease in premenopausal women.^[1-3]

In the present study cardiac parasympathetic reactivity to stress were done by performing the deep breathing test, Valsalva maneuver (VM) and lying-standing test to study the relationship of gender and lipid profile with cardiac parasympathetic reactivity.

MATERIALS AND METHODS

Sixty premenopausal and 60 postmenopausal women along with 60 young and 60 elderly, age and body mass index (BMI) matched men without any apparent illness were

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selected. Informed consent was taken. Permission from the ethical committee was obtained. This cross-sectional study was conducted in an industrial urban set up in a tertiary care hospital.

Inclusion criteria

Subjects were normotensive, nonobese, without any gross systemic disease and nonsmoker, and nonalcoholic. No persons were taking any sympathetic stimulant, blocker and Parasympathomimetics or lytics. All subjects were told to abstain from caffeine-containing beverages and drugs. Premenopausal females were examined during follicular phase of menstrual cycle.

Exclusion criteria

Subjects with any systemic, metabolic, or infectious disease were excluded. Females on oral contraceptives and estrogen replacement therapy were excluded.^[5] No pregnant subject was included. None of the subjects were taking any daily exercise or practicing yoga.

History was taken and general physical examinations were done. Resting pulse rate and blood pressure were recorded. Pretest instructions were given to avoid consumption of any drugs that may alter the autonomic functions. On the day of the test, no cigarette, nicotine, coffee, or drugs were permitted. All tests were performed at room temperature of 25°C between 10 am and 11 am.

Body weight and height were measured. The BMI was calculated and lipid profiles were analyzed by methods described below. Early morning venous samples were collected in plain bulbs from the subjects for analysis of lipid profile following a 12 hours overnight fasting. Samples were collected, centrifuged, and analyzed on the same day.

- i. HDL analysis: Enzymatic end point method was used. Noninsulin-dependent diabetes mellitus (ASPEN) HDL: Cholesterol test employs a specific antibody and is applied on an automated analyzer
- ii. Total cholesterol analysis: Phenol free cholesterol reagent was used
- iii. Triglyceride analysis: Dynamic extended stability with lipid clearing agent was used
- iv. LDL analysis: Enzymatic end point method was used. ASPEN LDL: Cholesterol test was employed.

Cardiac parasympathetic reactivity to stress

During postural change (30:15 R-R intervals ratios), deep breathing, VR. Apparatus: Polyrite-D, timer and modified mercurial sphygmomanometer. Polyrite is an electrical device with multi-channel physiograph. It has a built in electrocardiograph (ECG) channel for recording electrocardiogram.^[6]

Recording

Lead II of the ECG was selected for recording heart rate. Tracing speed used was 30 mm/s. Heart rate was recorded in supine position by conventional method during normal quiet breathing for a period of 1 min. The ECG tracings were screened for any suspected pathological waveform configuration.

Heart rate response to postural change (30:15 ratios)

After a complete rest of 15 min the ECG recording was started. The subject was instructed to stand erect from the supine position as quickly as possible (within 3 s) with continuous ECG recording for at least 30 s. The ratio of the longest R-R around 30th beat after standing to the shortest R-R interval around 15th beat after standing were calculated for result of 30:15 ratio (normal ≥ 1.04).

Heart rate variation during deep breathing

After a 5 min rest, the patient was instructed to take deep inspiration over 5 s and followed by expiration over next 5 s for 1 min. The difference of the heart rate between the maximum in the inspiratory cycle and the minimum in the expiratory cycles was calculated as result of the test (normal ≥ 15). Expiration:inspiration ratio was also calculated.

Procedure

The subject was asked to breathe deeply at a rate of 6 breaths/min, allowing 5 s each of expiration and inspiration. The maximum and minimum heart rate with each respiratory cycle and the mean variation was determined. The expiratory (E) to inspiratory (I) ratio was determined as sum of six longest R-R intervals divided by the sum of six shortest R-R intervals.

Heart rate response to valsalva maneuver

The test was done after 5 min of rest. The subject was instructed to exhale forcefully through the mouth piece of a modified mercurial sphygmomanometer and to maintain pressure in the manometer up to 40 mmHg for 15 s. ECG recording were taken during the maneuver and continued for about 30 s after the performance. The ratio of the longest R-R interval after blowing to the shortest R-R interval during blowing was calculated (normal ≥ 1.21).

Statistical analysis

Analysis was done using SPSS version 12.0. Values were recorded as mean and standard deviation (mean (SD)). One way analysis of variance (ANOVA) and the appropriate post-hoc comparison was done to determine statistically significant differences. Pearson's correlation coefficient was calculated between the independent variable (lipid profile parameters) and the dependent variables (deep breath test, Valsalva ratio, 30:15 R-R interval ratio) to understand the effect of lipid profile on autonomic control of heart. For all

analysis probability values (P value) $<0.05^*$ were considered statistically significant and $P<0.01^{**}$ were considered as statistically highly significant.

RESULTS

Significant differences were observed among all parameters when ANOVA was done among the four groups [Table 1]. Lipid profile showed significant increase in values of total cholesterol, LDL, triglyceride, and significant decrease in HDL values in younger male individuals when compared with premenopausal females and this difference disappeared with age and menopause. Resting pulse rate and systolic blood pressure were significantly increased in young males as compared with young females. Cardiac parasympathetic function tests during deep breath test and 30:15 R-R interval ratios showed significant decrease in younger males when compared with premenopausal females [Table 2]. When comparison was done between elderly males and elderly females no significant differences in resting pulse rate, blood pressure, parasympathetic function tests, and lipid profile were noticed [Table 2]. Tables 3-6 show that total cholesterol, triglyceride, LDL are negatively correlated with parasympathetic function tests; whereas HDL is positively correlated with parasympathetic function tests.

DISCUSSION

In the present study resting pulse rates and systolic blood pressures were significantly increased in younger males as compared with premenopausal females. Deep breath test, 30:15 R-R intervals ratio were also significantly decreased in males. In 2001, Weitz *et al.* found that the activity of sympathetic nervous system shows gender specific differences with lower sympathoneural activity to the muscle vascular bed in women, as compared with men, with this difference vanishing after menopause.^[7] In 2001, Higashi *et al.* showed that both menopause and hypertension are associated with endothelial dysfunction and are risk factors for coronary heart disease.^[8] Tanaka *et al.*, in 2003, observed that baroreceptor control of heart rate is altered during the regular menstrual cycle, and estradiol appears to exert cardiovagal modulation in healthy women.^[5] Liu *et al.*, in 2003, showed that women who were premenopausal had higher vagal but lower sympathetic modulations of HR than the age-matched men did, whereas these gender-related autonomic differences disappeared in the elderly.^[3] In 2009, Shailaja *et al.* concluded that both aging and declined estrogen levels are associated with the autonomic alterations seen among postmenopausal women.^[9]

Lower HRV was proven to be associated with a greater risk

Table 1: Average values and differences among all parameters when ANOVA was done among the four groups

Name of parameters	Different gender and age groups				
	Young females	Young males	Elderly females	Elderly males	P value
Age (years)	38.1 (2.5)	38.2 (2.5)	53.6 (8.7)	53.6 (8.5)	$<0.001^{**}$
BMI (kg/m^2)	20.8 (2.2)	20.9 (2.3)	22.8 (4.2)	22.9 (3.546)	0.021*
Pulse rate (beats/min)	74.1 (5.3)	77.7 (5.9)	80.3 (5.9)	80.9 (5.6)	0.001**
Systolic BP (mm of Hg)	123 (4.9)	126.1 (6.4)	127.4 (16.6)	127.4 (15.9)	0.006**
Diastolic BP (mm of Hg)	79.9 (5.7)	81.1 (6.0)	77.2 (8.9)	77.9 (8.8)	0.012**
Valsalva ratio	1.4 (0.1)	1.4 (0.1)	1.2 (0.1)	1.2 (0.1)	$<0.001^{**}$
Deep breath test (beats/min)	29.6 (4.1)	25.3 (4.5)	13 (8.6)	12 (4.8)	$<0.001^{**}$
Expiration: Inspiration ratio	1.44 (0.1)	1.3 (0.1)	1.2 (0.1)	1.2 (0.18)	$<0.001^{**}$
30:15 R-R ratio	1.14 (0.06)	1.11 (0.03)	1.1 (0.9)	1.1 (0.64)	$<0.001^{**}$
Cholesterol (mg/dl)	142.67 (19.01)	153.3 (21.29)	184 (24)	174 (24.7)	0.001**
Triglyceride (mg/dl)	106.7 (12.4)	112.3 (11.8)	119.13 (30.91)	120.73 (37.56)	0.015*
HDL (mg/dl)	52 (4.2)	45.6 (6.1)	49.37 (8.64)	49.47 (6.37)	0.036*
LDL (mg/dl)	68.43 (8.75)	72.6 (9.7)	106.03 (28.37)	110.63 (28.5)	0.001**

$P<0.05^*$ (significant); $P<0.01^{**}$ (highly significant)

Table 2: Multiple comparison (post-hoc)

Variables	Young females Vs.	Elderly males Vs.	Young females Vs.	Elderly males Vs.	Elderly females Vs.	Elderly males Vs.
	Young males	Elderly females	Elderly females	Young males	Young males	Young females
Age (years)	0.970	0.840	<0.001	<0.001	<0.001	<0.001
BMI (kg/m^2)	0.740	0.880	0.006	<0.001	<0.001	<0.001
Pulse (beats/min)	0.008	0.585	<0.001	<0.001	<0.001	<0.001
Systolic BP (mm of Hg)	0.004	0.973	0.047	0.004	0.005	0.004
Diastolic BP (mm of Hg)	0.623	0.973	0.012	0.025	0.125	0.012
Valsalva ratio	0.369	0.370	<0.001	<0.001	<0.001	<0.001
Deep breath test (beats/min)	<0.001	0.084	<0.001	<0.001	<0.001	<0.001
Expiration: Inspiration	<0.001	0.229	<0.001	<0.001	<0.001	<0.001
30:15 R-R ratio	0.002	0.254	<0.001	<0.001	<0.001	<0.001
Cholesterol	<0.001	0.070	<0.001	<0.001	<0.001	<0.001
TG	0.008	0.420	0.003	0.003	0.003	0.003
HDL	<0.001	0.480	0.013	0.013	0.013	0.013
LDL	0.017	0.267	<0.001	<0.001	<0.001	<0.001

P values for Table 1a

Table 3: Correlation of total cholesterol and parasympathetic function tests

Name of parameters	r value	
	Males	Females
Valsalva ratio	-0.51524	-0.5664
Deep breath test	-0.58007	-0.5131
30:15 R-R ratio	-0.55121	-0.5089

Table 4: Correlation of triglyceride and parasympathetic function tests

Name of parameters	r value	
	Males	Females
Valsalva ratio	-0.402	-0.40205
Deep breath test	-0.36514	-0.35623
30:15 R-R ratio	-0.277	-0.27742

Table 5: Correlation of LDL and parasympathetic function tests

Name of parameters	r value	
	Males	Females
Valsalva ratio	-0.58	-0.58218
Deep breath test	-0.70487	-0.68148
30:15 R-R ratio	-0.5303	-0.5331

LDL – Low density lipoprotein

Table 6: Correlation of HDL and parasympathetic function tests

Name of parameters	r value	
	Males	Females
Valsalva ratio	0.1532	0.153221
Deep breath test	0.274745	0.225104
30:15 R-R ratio	0.226	0.226067

HDL – High density lipoprotein

for developing hypertension among normotensive men, and hypertension is one of the major risk factor of CHD.^[2,3]

Total cholesterol, triglyceride, and LDL were negatively correlated with parasympathetic function tests; whereas HDL was positively correlated with parasympathetic function tests in the present study. Total cholesterol, triglyceride, and LDL cholesterol were found to be significantly increased and HDL cholesterol significantly decreased in younger males as compared with premenopausal females.

Hypercholesterolemia has been proved to be associated with a decreased 24 hours HRV in men with or without CHD. Baroreceptor sensitivity is negatively correlated with LDL cholesterol levels. The impaired endothelium dependent arterial dilatation in vessel walls caused by higher lipid levels might also change the baroreflex capacity.^[2]

Estrogen prevents cardiovascular diseases in several ways. It increases HDL cholesterol (particularly HDL 2) and decreases LDL and total cholesterol. It inhibits platelets and macrophage (foam cells) aggregation at the vascular intima. It stimulates the release of nitric oxide and prostacycline from vascular endothelium to dilate blood vessels. It prevents atherosclerosis by its antioxidant properties.^[1,2]

Strengths of study

Premenopausal women,^[1] as compared with young men showed better responses to parasympathetic function tests. They also had decreased values of total cholesterol, LDL, triglyceride, and significantly increased values of HDL as compared with young males. Total cholesterol, triglyceride, LDL were negatively correlated with parasympathetic function tests; while HDL was positively correlated with parasympathetic function tests in the present study This study identified an increasing need for nationwide efforts to develop various intervention programs for surveillance of increasing geriatric health problems.

Limitations of study

The sample was drawn from one limited geographic area; the results cannot properly be generalized to the national population. Second, because of the cross-sectional design, this study had limited extrapolative value.

CONCLUSION

Sex hormone levels may alter the autonomic nervous system response and lipid metabolism and lipids play an important role in modulation of autonomic functions.

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