# Evaluation of Association Between Hyperlipidemia and Heart Rate Variability in Subjects Without Apparent Cardiovascular Disease

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## ABSTRACT

**Introduction:** There is limited data in the literature regarding the association between hyperlipidemia and heart rate variability (HRV). The aim of the present study is to investigate the association between HRV and hyperlipidemia by retrospectively evaluating the recordings of subjects free of any apparent cardiovascular or systemic disease.

**Patients and Methods:** Medical records of patients to whom 24 hour-Holter recording was performed in our clinic between January 2012 and May 2013 were retrospectively examined. Data of subjects who were determined to be free of any cardiovascular or systemic disease were used in the analysis.

**Results:** Data of 37 subjects were used. There were 20 subjects with hyperlipidemia (10 male, age: 44.5 ± 11.1 years) and 17 subjects with normal lipid profile (5 male, age: 33.4 ± 10.6 years; p= 0.18 for gender and p=0.004 for age). Majority of HRV parameters were found to be significantly depressed in group with hyperlipidemia; however, there were no significant difference between groups regarding prevalence of arrhythmias. Out of components of the lipid profile, linear regression analysis revealed serum triglyceride level to be independently associated variable with RMSSD, PNN50 and LF/HF ratio (in respective order; beta= -0.40, p= 0.02; beta= -0.41, p= 0.012 and beta= -0.31, p= 0.05).

**Conclusion:** Subjects with hyperlipidemia were observed to have significantly depressed HRV compared to subjects with normal lipid profile in our retrospective study. Based on our observations, it may be suggested that patients with hyperlipidemia, in particular with hypertriglyceridemia display higher subtle cardiac sympathetic activity which may be associated with increased cardiovascular morbidity and mortality.

**Key Words:** Hyperlipidemia; holter recording; heart rate; autonomic nervous system

## Bilinen Kardiyovasküler Hastalığı Olmayan Kimselerde Hiperlipidemi ve Kalp Hızı Değişkenliği Arasındaki İlişkinin Araştırılması

## ÖZET

**Giriş:** Literatürde hiperlipidemi ve kalp hızı değişkenliği (KHD) ilişkisiyle ilgili sınırlı sayıda veri mevcuttur. Çalışmamızın amacı aşikâr kardiyovasküler veya sistemik hastalığı olmayan bireylerin kayıtlarını retrospektif olarak inceleyerek KHD ve hiperlipidemi arasındaki ilişkiyi araştırmaktır.

**Hastalar ve Yöntem:** Ocak 2012 ve Mayıs 2013 tarihleri arasında kliniğimizde 24 saatlik Holter tetkiki yapılan tüm hastaların medikal kayıtları incelendi. Sistemik veya kardiyovasküler hastalığı olmadığına karar verilen kişilerin verileri analizde kullanıldı.

**Bulgular:** Toplam 37 kişinin verisi kullanıldı. Yirmi kişinin hiperlipidemik (10 erkek, yaş: 44.5 ± 11.1) olduğu saptanırken 17 kişinin normal lipit profiline sahip olduğu izlendi (5 erkek, yaş: 33.4 ± 10.6; cinsiyet için p= 0.18 ve yaş için p= 0.004). Hiperlipidemik hasta grubunda normal lipit profili grubuna göre çoğu KHD parametresinin anlamlı derecede deprese olduğu izlendi ancak aritmi prevalansları arasında fark saptanmadı. Lineer regresyon analizinde serum trigliserid düzeyinin RMSSD, PNN50 ve LF/HF oranı ile bağımsız olarak ilişkili olduğu görüldü (sıra ile beta= -0.40, p= 0.02; beta= -0.41, p= 0.012 ve beta= -0.31, p= 0.05).

**Sonuç:** Retrospektif çalışmamız sonucunda hiperlipidemisi olan grupta normal lipit profili olan kişilere göre kalp hızı değişkenliğinin anlamlı derecede deprese olduğu gözlendi. Gözlemlerimiz sonucunda özellikle hipertrigliseridemisi olan hiperlipidemik kişilerin daha yüksek kardiyak sempatik aktivite gösterdikleri ve bu durumun artmış kardiyovasküler morbidite ve mortalite ile ilişkili olabileceği düşünülebilir.

**Anahtar Kelimeler:** Hiperlipidemi; holter kaydı; kalp hızı; otonom sinir sistemi

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## INTRODUCTION

The relationship between alterations in autonomic nervous system activity and cardiovascular morbidity and mortality is well established[1-4]. Heart rate variability (HRV) is a statistical measure of the cyclic beat-to-beat variation, and has been shown to be a useful non-invasive tool for assessing the cardiac autonomic function. Attenuation in HRV is associated with increased sympathetic and decreased parasympathetic activity[5]. Numerous studies have demonstrated that these alterations are associated with higher cardiovascular risk both in patients with established cardiovascular disease and in apparently healthy subjects[1-5]. Several physiological and pathological conditions may alter HRV[5].

There is limited data in the literature regarding the association between hyperlipidemia and HRV. However, available data suggest that hyperlipidemia is associated with a depressed HRV in subjects with and without coronary artery disease[6]. Partial reversibility of these alterations with lipid lowering drugs has also been proposed[7,8].

The aim of the present study is to investigate the association between HRV and hyperlipidemia by retrospectively evaluating serum lipid profiles and 24 hour-Holter recordings of subjects who had admitted to our clinic and found to be free of any apparent cardiovascular or systemic disease.

## MATERIAL and METHODS

### Subjects

Medical records of patients to whom 24 hour-Holter recording was performed in our clinic between January 2012 and May 2013 were retrospectively examined (n= 1005). Patients with available transthoracic echocardiography recordings which demonstrated normal echocardiographic examination were selected from the study population (n= 62). Patients with any evidence of ischemic heart disease, abnormal electrocardiogram (ECG) and abnormal serum biochemisty, complete blood count or thyroid function tests were excluded from the study. Other exclusion criteria were history of hypertension, diabetes mellitus, smoking, peripheral arterial disease and usage of any kind of medication at the time of 24 hour-Holter recording. After exlusion of these patients, Holter data of 37 subjects were examined and used in the analysis.

### Serum Lipid Profile

Fasting serum total cholesterol, low-density lipoprotein level (LDL), high-density lipoprotein level (HDL) and triglyceride level of all subjects were noted. Serum cholesterol, HDL-C and triglycerides had been measured by a Beckman-Coulter automated chemistry analyzer using Beckman-Coulter reagents (Brea, CA, USA). LDL had been calculated by using the Friedewald Formula. Subjects were assumed to have hyperlipidemia if their fasting total serum cholesterol was more than 200 mg/dl, and/or their serum triglyceride level was over 200 mg/dl, and/or their serum LDL level was over 130 mg/dL.

### Analysis of Heart Rate Variability Parameters

24-hour Holter monitorings had been obtained using DMS300-3A (California, USA) 5-channel digital recorders and analyzed by using available software (Cardioscan 12.0, DMS, USA). Holter recordings had been performed to these subjects due to variety of reasons in our clinic but the most frequent reason was to evaluate the complaint of palpitation. The time and frequency domain analysis of HRV were performed according to the recommendation of the European Society of Cardiology task force[9]. The minimum-, maximum- and mean heart rate, standard deviation of all NN intervals (SDNN), standard deviation of the averages of NN intervals in all 5 min segments of the entire recording (SDANN), root mean square of successive differences (RMSSD) and percentage of differences between successive NN intervals over 24 hours that is greater than 50 ms (PNN50) were measured in the time domain analysis of HRV. SDNN has been assumed to reflect overall HRV. While SDANN has been assumed to reflect HRV's long-term components, RMSSD and PNN50 have been assumed to reflect its short-term components[9]. A diminished SDNN has been considered to reflect a reduced autonomic modulation of sinus node. The power spectrum of HRV was measured using fast-Fourier transform analysis in three frequency bands: < 0.04 Hz (very low frequency, VLF), 0.04-0.15 Hz (low frequency, LF) and 0.15-0.4 Hz (high frequency, HF). HF has been used as a marker of the activity of parasympathetic nervous system and LF has been used as a marker of both sympathetic and parasympathetic activity. The ratio of low- high frequency power (LF/HF) has been assumed to be a marker of the sympathovagal balance[5,9].

### Statistical Analysis

Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 11.0 was used for data analysis. Distribution of data was assessed by using one-sample Kolmogorov-Smirnov test. Values displaying normal distribution were expressed as the mean ± SD and values not displaying normal distribution were expressed as median (interquartile range). For comparison of categorical variables or percentages, we used Fisher's exact test. Differences between numeric variables were tested with independent samples Student's t-test. Correlation was tested by Pearson or Spearman's correlation tests where appropriate. Linear regression analysis was used to define independently associated variables with LF/HF ratio, RMSSD and PNN50. Age, body mass index (BMI), serum total cholesterol, LDL, HDL and triglyceride level were selected as dependent variables for multivariate analysis. A significance level was set at $p< 0.05$.

## RESULTS

Data of 37 subjects were used in the analysis. Serum glucose and electrolyte levels, liver-, renal- and thyroid function tests of all subjects were within normal limits. There were 20

subjects with hyperlipidemia and 17 subjects with normal lipid profile. There were 10 men (%50) in the group with hyperlipidemia and 5 men (%29.4) in the group with normal lipid profile (p= 0.18). Mean age of hyperlipidemic subjects was significantly higher compared with subjects with normal lipid profile (44.5 ± 11.1 vs 33.4 ± 10.6 years respectively, p= 0.004). There was no significant difference between hyperlipidemic and normal lipid profile groups regarding BMI (26.5 ± 2.6 vs 26.2 ± 5.9 kg/m2, respectively, p= 0.88). Serum lipid profiles of the groups are presented on Table 1.

On 24-hour-Holter recordings ventricular premature complexes (VPC) occurred in 6 subjects (%30) with hyperlipidemia and in 7 subjects (%41.7) with normal profile (p= 0.35). There was no significant difference between groups regarding the prevalence of frequent VPC's which was defined as VPC's more than 30 complexes/hour (2 subjects [%10] with hyperlipidemia and 3 subjects [%17.6] with normal lipid profile, p= 0.42). There were no subjects with ventricular tachycardia among the study population. Supraventricular premature complexes (SVPC) occurred in 6 subjects with hyperlipidemia (%20) and 2 subjects with normal lipid profile (%11.8) (p= 0.17). One subject with hyperlipidemia (%5.0) and 1 subject with normal lipid profile (%5.9) displayed paroxysmal atrial fibrillation in their 24-hour-Holter recordings (p= 0.72).

Heart rate variability (HRV) parameters of the groups are presented on Table 2. Majority of HRV parameters were found to be significantly depressed in group with hyperlipidemia (Table 2).

There was no significant correlation between SDNN and age, BMI or any component of lipid profile. The only significant correlated variable with SDNN index was age (r= -0.28, p= 0.03). However, significant correlations were found between RMSSD, PNN50 and age, total cholesterol, LDL and triglyceride level (Table 3). There were no significant correlations between any of HRV parameters and serum HDL level or BMI. Linear regression analysis revealed serum triglyceride level as the only independently associated variable with RMSSD and PNN50 (Beta coefficient: -0.40, %95 CI -0.17- -0.02, p= 0.016 and beta coefficient: -0.41, %95 CI -0.12- -0.02, p= 0.012; respectively).

There were significant negative correlations between LF/HF ratio and age (r = -0.52, p< 0.001), total cholesterol (r= -0.49, p : 0.02), LDL (r= -0.35, p: 0.03) and triglyceride levels (r= -0.31, p: 0.05). Linear regression analysis revealed

**Table 1. Comparison of lipid profiles of subjects with and without hyperlipidemia**

| | Subjects with hyperlipidemia (n= 20) | Subjects with normal lipid profile (n= 17) | p value |
|---|---|---|---|
| Total cholesterol (mg/dL) | 229.3 ± 49.6 | 159.6 ± 25.2 | 0.001 |
| LDL (mg/dL) | 136.8 ± 44.7 | 83.9 ± 20.9 | <0.001 |
| HDL (mg/dL) | 49.7 ± 17.5 | 52.8 ± 14.4 | 0.562 |
| Triglyceride (mg/dL) | 159.5 ± 79.4 | 104.5 ± 45.4 | 0.016 |

LDL: Low density lipoprotein, HDL: High density lipoprotein

**Table 2. Comparison of heart rate variability parameters of subjects with and without hyperlipidemia**

| | Subjects with hyperlipidemia (n= 20) | Subjects with normal lipid profile (n= 17) | p value |
|---|---|---|---|
| Maximum heart rate (/min) | 141.6 ± 13.2 | 146.6 ± 18.9 | 0.35 |
| Minimum heart rate (/min) | 55.7 ± 14.2 | 50.2 ± 13.2 | 0.23 |
| Mean heart rate (/min) | 81.0 ± 10.3 | 77.2 ± 6.3 | 0.20 |
| SDNN (msec) | 129.9 ± 44.0 | 156.3 ± 42.1 | 0.073 |
| SDANN (msec) | 120.1 ± 44.3 | 146.8 ± 43.3 | 0.074 |
| RMSSD (msec) | 47.1 ± 13.1 | 64.2 ± 15.5 | 0.001 |
| pNN50 (%) | 23.1 ± 10.1 | 33.7 ± 10.6 | 0.004 |
| VLF ($ms^2$/Hz) | 1696.2 ± 937.7 | 2919.3 ± 1622.2 | 0.007 |
| LF ($ms^2$/Hz) | 427.9 ± 229.1 | 919.9 ± 428.2 | <0.001 |
| HF ($ms^2$/Hz) | 178.2 ± 236.0 | 345.6 ± 231.5 | 0.037 |
| LF/HF ratio | 4.5 ± 5.8 | 10.9 ± 7.4 | 0.006 |

SDNN: Standard deviation of all NN intervals, SDANN: Standard deviation of the averages of NN intervals in all 5 min segments of the entire recording, RMSSD: Root mean square of successive differences, PNN50: Percentage of differences between successive NN intervals over 24 hours that are greater than 50 ms, VLF: Very low frequency, LF: Low frequency, HF: High frequency

**Table 3. Bivariate correlation analysis between RMSSD, PNN50 and age and components of lipid profile**

| | Age | Total cholesterol level | LDL level | Triglyceride level |
|---|---|---|---|---|
| RMSSD | r = -0.43<br>p= 0.001 | r = -0.46<br>p= 0.004 | r = -0.36<br>p= 0.027 | r = -0.36<br>p= 0.026 |
| PNN50 | r = -0.24<br>p= 0.064 | r = -0.45<br>p= 0.005 | r = -0.36<br>p= 0.028 | r = -0.39<br>p= 0.015 |

LDL: Low density lipoprotein, RMSSD: Root mean square of successive differences, PNN50: Percentage of differences between successive NN intervals over 24 hours that is greater than 50 ms

age (Beta coefficient: -0.41, %95 CI -0.43 - -0.06, p= 0.01) and serum triglyceride level (Beta coefficient: -0.31, %95 CI -0.06-0.00, p= 0.05) as the independently associated variables with LF/HF ratio.

## DISCUSSION

Subjects with hyperlipidemia were observed to have significantly depressed HRV compared with the ones with normal lipid profile in our retrospective study. However, there was no significant difference between groups regarding the prevalence of arrhythmias on 24-hour Holter recordings. Only age and serum triglyceride level was found to be independently associated variables with LF/HF ratio which is assumed to be a marker of sympathovagal balance. Serum triglyceride level was also the only parameter which is independently associated with short term components of HRV derived from time-domain analysis. As such, it may be suggested that patients with hyperlipidemia, in particular with hypertriglyceridemia display higher subtle cardiac sympathetic activity which may be associated with increased cardiovascular morbidity and mortality.

A number of studies have examined the association between hyperlipidemia and HRV. In a sample of 88 healthy persons, Kupari et al. found inverse relationship between HRV and LDL cholesterol levels[10]. However, only short-term HRV was measured in this study. We studied both short term and long term components of time domain HRV analysis in addition to the frequency domain analysis. In contrast with the observations of Kupari et al. there were no significant independent association between serum LDL levels and any of HRV parameters in our study. In another study by Christensen et al., hyperlipidemia was associated with a decreased HRV both in men with and without ischemic heart disease[6]. They found age, BMI and plasma cholesterol as independently associated variables with SDNN index. They didn't find any correlation between serum triglyceride level and time domain HRV parameters in men with ischemic heart disease. Serum triglyceride level was correlated only with mean RR interval in healthy men but not with any other HRV parameter. In contrast with the observations of Christensen et al, serum triglyceride level was found to be independently associated with majority of HRV parameters in our study and only age was found to be significantly correlated with SDNN index.

Later studies also investigated the effect of lipid lowering therapies on HRV. Melenovsky et al. suggested that combined hyperlipidemia was associated with decreased HRV which was partially reversible with statins and fibrates[8]. This observation was in agreement with the findings of a previous study in which long-term atorvastatin therapy in hypercholesterolemic subjects led to an increase in time-domain parameters of HRV[7].

The mechanism of association between hyperlipidemia and depressed HRV is not clear at the moment. It is known that catecholamines can influence lipid metabolism causing increased lipolysis and free fatty acid (FFA) mobilization[11]. Consequent upon the increased FFA mobilization, there is increased uptake of FFA into tissues which leads to increased hepatic secretion of triglyceride rich lipoproteins into plasma leading to increase in serum triglyceride levels. As such, increased sympathetic activity might have affected both serum lipids and HRV of subjects who were analyzed in our retrospective study. Epidemiological evidence indicates that serum triglyceride level is independently associated with the risk of cardiovascular disease[12,13]. Based on our observations, it may be suggested that subtle alterations in cardiac autonomic activity present in hypertriglyceridemic subjects might be a contributing factor to the increased risk related with hypertriglyceridemia.

### Study Limitations

Inherent limitations of retrospective studies are also valid for our study. Patients without available transthoracic echocardiographic recordings were excluded from the analysis. As such, data of only a limited sample of study population could be used in our analysis. However, the independent association between serum triglyceride level and HRV was evident even in this limited sample of study population.

### Conclusion

Subjects with hyperlipidemia were observed to have significantly depressed HRV compared to subjects with normal lipid profile in our study. Out of lipid profile components only serum triglyceride level was found to be independently associated with short term time-domain components of HRV and LH/HF ratio. Based on these observations it may be suggested that serum triglyceride level may also be considered as a marker of increased sympathetic activity during determination of cardiovascular risk in asymptomatic subjects.

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## CONFLICT of INTEREST

The authors reported no conflict of interest retaled to this article.

## AUTHORSHIP CONTRIBUTIONS

*Concept/Design:* AK, AÇ, BM, OE
*Analysis/Interpretation:* AK, ZD, CM
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