



Subclinical Left Ventricular Dysfunction in Chronic Asymptomatic Alcoholic Patients

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ABSTRACT

Introduction: The aim of this study was to use speckle-tracking echocardiography (STE) for identifying subclinical global systolic function abnormalities in chronic asymptomatic alcoholic patients with a normal ejection fraction.

Patients and Methods: We included 30 healthy subjects (age 34.8 ± 5.8 years) and 75 asymptomatic alcoholic patients (age 39.8 ± 6.5 years) and divided them into two groups according to their total lifetime dose of ethanol (TLDE): group I (TLDE < 15 kg ethanol/kg body weight) and group II (TLDE ≥ 15 kg ethanol/kg body weight). In the two-dimensional (2D)-STE analysis, the left ventricular (LV) global longitudinal strain (G-LS), longitudinal global strain rate in systole (G-SRsys), longitudinal global strain rate in early diastole (G-SRearly) and longitudinal global strain rate in late diastole (G-SRlate) values were obtained.

Results: Alcoholic patients had larger end-systolic and end-diastolic dimensions, thicker interventricular septal and posterior wall and higher LV mass index. However, there were no differences in the end-systolic and end-diastolic dimensions and LV mass index among them. The ejection fraction did not differ between the groups. The G-LS values were lower in alcoholic patients ($p < 0.001$). G-LS was found to be significantly lower among alcoholic patients, although the LV mass index and LV dimensions remained unchanged. Although G-SRsys was lower in alcoholic patients compared with that in controls ($p = 0.03$), there were no differences in the G-SRearly and G-SRlate values. There was a significant correlation between G-LS values and TLDE ($r = 0.49$, $p < 0.001$).

Conclusion: To the best of our knowledge, this is the first study demonstrating the presence of early functional abnormalities of longitudinal systolic function by 2D-STE in chronic alcoholic patients. These functional mechanics have a parallel impairment with the increase in alcohol consumption.

Key Words: Alcoholic patients; left ventricular dysfunction; echocardiography; speckle tracking

Kronik Asemptomatik Alkolik Hastalarda Subklinik Sol Ventrikül Disfonksiyonu

ÖZET

Giriş: Bu çalışmanın amacı, normal sol ventrikül ejeksiyon fraksiyonu olan asemptomatik kronik alkolik hastalarda subklinik global sistolik fonksiyon bozukluğu olup olmadığını "speckle tracking ekokardiyografi (STE)" yöntemini kullanarak araştırmaktır.

Hastalar ve Yöntem: Çalışmaya, 30 sağlıklı hasta (ortalama yaş 34.8 ± 5.8 yıl) ve 75 asemptomatik alkolik hasta (ortalama yaş 39.8 ± 6.5 yıl) alındı ve bu hastalar yaşamı boyunca aldığı etanol miktarına (TLDE) göre iki gruba ayrıldı: grup I (TLDE < 15 kg etanol/vücut ağırlığı-kg) ve grup II (TLDE ≥ 15 kg etanol/vücut ağırlığı-kg). İki boyutlu STE analizinde, sol ventrikül (LV) global longitudinal strain (G-LS), sistolde longitudinal global strain rate (G-SRsys), erken diyastolde longitudinal global strain rate (G-SRearly) ve geç diyastolde longitudinal global strain rate (G-SRlate) değerleri hesaplandı.

Bulgular: Alkolik hastalarda, sistol sonu ve diyastol sonu çapların daha geniş, interventriküler septum ve posterior duvarın daha kalın ve LV kitle indeksi değerlerinin daha yüksek olduğu saptandı. Ancak, alkolik hastalar arasında sistol sonu ve diyastol sonu çaplar ve LV kitle indeksi değerleri açısından anlamlı bir farklılık saptanmadı. Gruplar arasında LV ejeksiyon fraksiyonu açısından farklılık yoktu. Alkolik hastalarda G-LS değerleri daha düşüktü ($p < 0.001$). LV kitle indeksi ve LV çaplarında anlamlı farklılık olmamasına rağmen, G-LS değerlerinin alkolik hastalarda belirgin düzeyde daha düşük olduğu gösterildi. Kontrol grubu ile kıyaslandığında, G-SRsys değerlerinin alkolik hastalarda daha düşük olduğu ancak G-SRearly ve G-SRlate değerlerinde farklılık olmadığı saptandı. G-LS değerleri ile TLDE arasında anlamlı bir korelasyon olduğu gösterildi ($r = 0.49$, $p < 0.001$).

Sonuç: Bildiğimiz kadarıyla çalışmamız literatürde, kronik alkolik hastalarda 2D-STE ile değerlendirmede longitudinal sistolik fonksiyonlarda erken bozulmanın olduğunu gösteren ilk çalışmadır. Bu fonksiyonel mekanikler, alkol tüketiminin artışına paralel olarak bozulmaktadır.

Anahtar Kelimeler: Alkolik hastalar; sol ventrikül disfonksiyonu; speckle tracking

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INTRODUCTION

Chronic excessive alcohol consumption causes destructive and diffuse effects on the myocardium, independent of coronary atherosclerosis, hypertension or valvular disease⁽¹⁾. Although left ventricular (LV) dysfunction is a frequent finding among chronic alcoholic patients, it would be crucial to find a method for the reliable detection of LV dysfunction onset in chronic asymptomatic alcoholic patients before irreversible damage occurs⁽²⁾.

Recently, a two-dimensional speckle-tracking echocardiography (2D-STE) technique that is independent of the ultrasound angle of interrogation has been developed, allowing a non-invasive measurement of the overall LV strain⁽³⁾. Therefore, this method can provide a new mechanistic insight into systolic dysfunction even in patients without structural cardiac changes (stage A of the ACC/AHA classification of heart failure)⁽⁴⁾.

Identifying subclinical LV systolic dysfunction among chronic alcoholic patients might be helpful in identifying patients at higher risk of heart failure. For this purpose, we used a more contemporary echocardiographic method, 2D-STE, to better investigate LV functions. This study aimed to analyze the LV mechanics in chronic asymptomatic alcoholic patients using 2D strain and evaluate the possible differences in LV systolic function, as assessed by 2D-STE, related to the total lifetime dose of ethanol (TLDE).

PATIENTS and METHODS

Study Population

Seventy-five consecutive asymptomatic male alcoholic patients (age 39.8 ± 6.5 years, range 31-55 years) who were admitted to our outpatient alcoholism unit for assistance in terminating their dependence on alcohol were enrolled in this study. The study protocol was approved by the institutional review board of Kosuyolu Heart and Research Hospital, and each subject provided written informed consent to participate.

Inclusion criteria were 1) positive diagnosis for alcohol abuse according to the criteria established by the American Psychiatric Association, 2) daily ethanol consumption of ≥ 90 g and ≥ 4 days/week and 3) drinking history of ≥ 5 years⁽⁵⁾. Exclusion criteria were 1) impairment of the LV systolic function (ejection fraction, EF $< 50\%$) in echocardiographic evaluation, 2) patients with a history of coronary artery disease (CAD, defined as any degree of CAD on a previous angiogram or history of myocardial infarction or angina) and 3) patients with chronic liver disease or renal dysfunction.

All the patients and their families and friends were questioned by experienced psychiatrists about the total duration of their heavy alcohol consumption and the type and amount of drinks consumed per day. Daily ethanol consumption was obtained by converting the type and amount of alcoholic beverages to grams of absolute ethanol. Calculation of TLDE was expressed in kg of ethanol/kg of body weight and was estimated by first multiplying the daily consumption of ethanol by the number of days of exposure to alcohol and then dividing the product by the body weight of the patient when first admitted⁽⁶⁾. In addition to

data collection, it was decided to classify alcoholic patients into two groups according to the TLDE values: group I (TLDE < 15 kg ethanol/kg body weight) and group II (TLDE ≥ 15 kg ethanol/kg body weight).

The current smokers (more than 10 cigarettes consumed daily) were also recorded.

Thirty healthy male controls (age 34.8 ± 5.8 years, healthy controls vs. group I, $p = \text{NS}$, healthy controls vs. group II, $p \leq 0.001$) without drinking histories were evaluated as controls. None of them had a history of hypertension, diabetes mellitus and dyslipidemia or any history, signs and symptoms of cardiovascular disease.

Clinical and Laboratory Evaluations

A complete physical examination was performed for all patients. Anthropometric measurements of their height and weight were obtained, and their body mass index (BMI, kg/m²) and body surface area (BSA, m²) were calculated. Blood pressures were measured after 10 min of rest in a quiet room. Venous blood samples were obtained in the morning after 12-h fasting. Complete blood counts and biochemical parameters, such as haemoglobin, serum glucose, creatinine, total cholesterol and triglycerides, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were assessed.

No patient had palpitation, dyspnoea, chest pain or other symptoms suggestive of cardiovascular disease at the time of examination.

A 12-lead standard resting electrocardiogram and exercise treadmill stress testing according to the modified Bruce protocol were performed on all patients to exclude the presence of silent myocardial ischaemia or significant disturbances of the sinus rhythm. No patients had any abnormal test results.

Conventional, Pulsed Doppler and Tissue Doppler Echocardiographies

All the echocardiographic measurements were obtained using a commercially available ultrasound system (GE-Vivid 7 system, Horten, Norway) with a 3.5 MHz transducer. All data were transferred to a workstation for further offline analysis (EchoPAC, GE, Horten, Norway).

The LV end-diastolic diameter (EDD), end-systolic diameter (ESD), end-diastolic thickness of the interventricular septum (IVS) and end-diastolic thickness of the LV posterior wall (PW) were measured by M-mode echocardiography. Using these parameters, we calculated the LV mass (g). The left ventricular mass index was determined by dividing the LV mass measurement by the BSA (g/m²). Next, the LV end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were calculated from the apical two- and four-chamber views using a modified Simpson's method. The LV ejection fraction (EF) was calculated as $(\text{LVEDV} - \text{LVESV}) / \text{LVEDV} \times 100$.

The transmitral flow velocity was obtained from an apical four-chamber view with the pulsed Doppler method. After measuring the peak early (E) and late (A) diastolic velocities, the ratio of the early diastolic to late diastolic mitral inflow velocities (E/A) was calculated. Mitral annulus velocities were obtained from the septal and lateral annulus by tissue Doppler

imaging. Average mitral annulus velocities were calculated by averaging the septal and lateral mitral annulus velocities. All the measurements were obtained for three cardiac cycles and then averaged.

2D Strain Imaging

For deformation imaging analysis, we acquired standard greyscale 2D images from the four-chamber (4C), apical long axis (LAX) and two-chamber (2C) views using a high frame rate (50-90 frames/s). At each plane, three consecutive cardiac cycles were acquired at the end expiration of breath holding and stored digitally for offline analysis. Image analysis was performed offline on a PC workstation using a custom analysis software (EchoPac Software, GE Vingmed, Horten, Norway). A region of interest was traced on the endocardial cavity interface by a point-and-click approach from an end-systolic single frame. Subsequently, an automated tracking algorithm followed the endocardium from this single frame throughout the cardiac cycle. Further adjustment of the region of interest was performed to ensure that all the myocardial regions were included. Next, the speckles, equally distributed in the region of interest, could be followed throughout the cardiac cycle. Global longitudinal strain (GLS) and strain rate curves were obtained, including all six LV myocardial segments from the 4C, LAX and 2C views. The average values of the peak systolic longitudinal strain and the peak systolic strain rate from the three apical views were calculated as the global longitudinal strain (G-LS) and the global systolic strain rate (G-SR_{sys}), respectively. Similarly, the global strain rates during the early (G-SR_{early}) and late (G-SR_{late}) phases of diastole were calculated. Figure 1 shows an example

of GLS analysis in a healthy control (A) and in a patient from group II (B).

Statistical Analysis

Continuous and categorical variables are expressed herein as means \pm standard deviations (SD) and percentages, respectively. Continuous variables were compared using the one-way analysis of variance and are listed in Table 1. The Tukey test was applied for post hoc analyses. The analysis of covariance models included the systolic and diastolic hypertension and age as covariates to statistically control for baseline differences in these variables in Tables 2 and 3. Categorical variables were compared using the chi-square test (χ^2) or Fisher's exact test, as appropriate. Spearman's test was used for correlation analysis. A p-value of less than 0.05 was regarded as significant for all the analyses. All the statistical tests were performed using SPSS 11.5 (SPSS Inc., Chicago, IL, USA).

RESULTS

The demographic and clinical parameters of these three groups are shown in Table 1. The participants who consumed alcohol were all men, with a mean age of 39.8 ± 6.5 years (range 31-55 years). There were no differences in the number of smokers and the BMI values. However, there were differences in age, systolic and diastolic blood pressure and biochemical parameters (e.g. triglycerides, ALT, AST). Post hoc analysis showed that for age, healthy controls vs. group I, $p = \text{NS}$, healthy controls vs. group II, $p \leq 0.001$ and group I vs. group II, $p = 0.001$.

Table 1. General characteristics of the study participants

Variables	Healthy controls (n= 30)	Alcoholic patients (n= 75)		p value
		Group I (n= 43)	Group II (n= 32)	
Age (years)	34.8 \pm 5.8	37.5 \pm 5.7	42.7 \pm 6.4	< 0.001
Gender male (n, %)	30 (100)	43 (100)	32 (100)	NS
BMI (kg/m ²)	26.1 \pm 3.2	28.3 \pm 4.9	28.6 \pm 5.0	NS
Smokers (n, %)	13 (43.3)	25 (58.1)	18 (56.2)	NS
Systolic BP (mmHg)	119.9 \pm 8.4	124.9 \pm 10.6	133. \pm 16.5	0.001
Diastolic BP (mmHg)	75.5 \pm 5.4	81.5 \pm 8.8	85.0 \pm 11.9	0.004
Glucose (mg/dL)	92 \pm 10.8	95 \pm 14.7	94.8 \pm 13	NS
Total cholesterol (mmol/L)	171.6 \pm 29.2	191.1 \pm 36.3	199.4 \pm 61.1	NS
Triglycerides (mmol/L)	132.8 \pm 33.1	168.8 \pm 51.1	196.9 \pm 74.8	0.001
AST (U/L)	25.4 \pm 8.7	38.4 \pm 15.7	39.1 \pm 13.5	0.001
ALT (U/L)	27.0 \pm 10.3	40.4 \pm 14.4	43.9 \pm 22.1	0.002
Hemoglobin (g/dL)	14.2 \pm 1.4	14.6 \pm 1.3	14.7 \pm 2.2	NS
Drinking histories				
Duration of heavy drinking (year)	None	11.5 \pm 2.8	17.1 \pm 3.6	< 0.001
Daily ethanol consumption (g)	None	174.4 \pm 42.4	198.1 \pm 43.6	0.002
TLDE (kg ethanol/kg body weight)	None	10.3 \pm 3.1	17.0 \pm 1.5	< 0.001

BMI: Body mass index, BP: Blood pressure, AST: Aspartic acid transaminase, ALT: Alanine transaminase, TLDE: Total lifetime dose of ethanol.

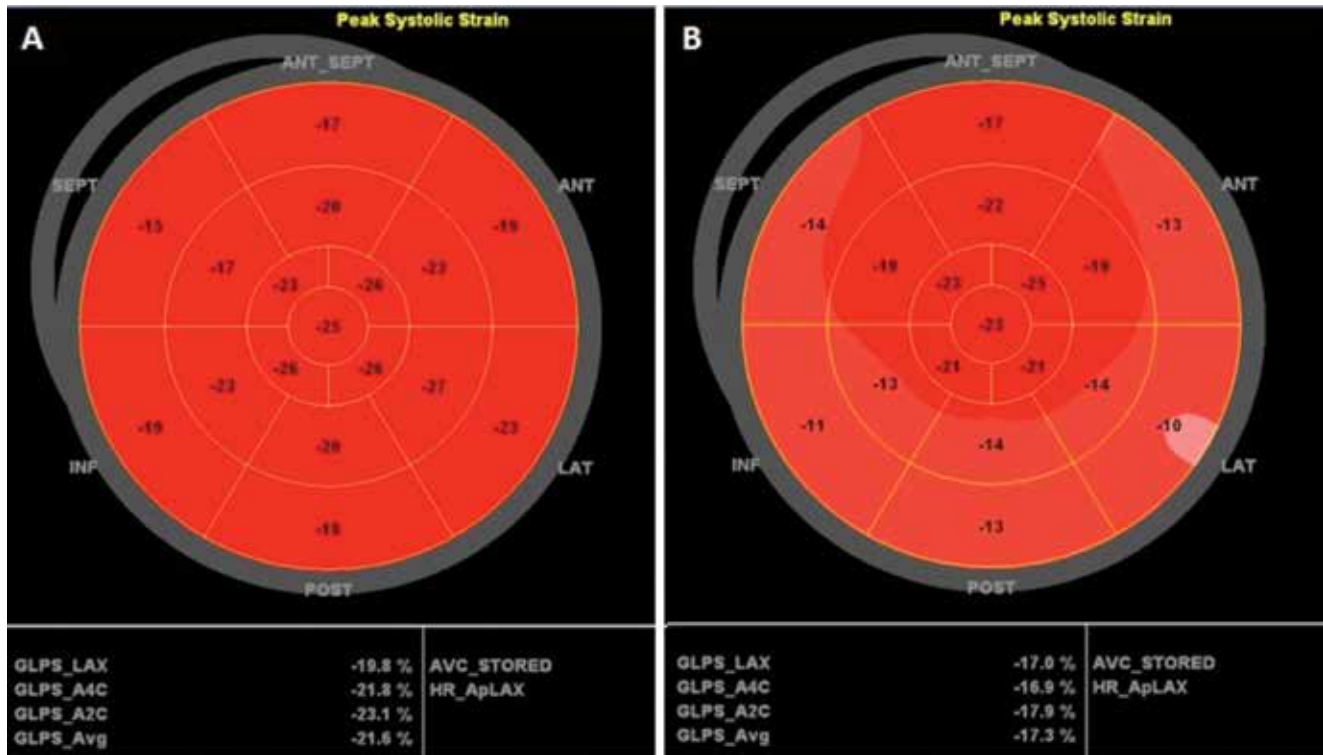


Figure 1. Example of a normal systolic peak of global longitudinal strain (G-LS) in a healthy control (A) and in a patient from group II (B).

Table 2. Echocardiographic measurements of LV geometry and function

Variables	Healthy controls (n= 30)	Alcoholic patients (n= 75)		p value*
		Group I (n= 43)	Group II (n= 32)	
LV-EDD (cm)	4.7 ± 0.4	4.9 ± 0.3	5.1 ± 0.3	0.005
LV-ESD (cm)	3.1 ± 0.3	3.3 ± 0.2	3.4 ± 0.2	0.008
LV-EF (%)	63.4 ± 4.7	60.7 ± 5.9	61.1 ± 4.9	NS
IVS (mm)	0.79 ± 0.11	0.88 ± 0.11	0.96 ± 0.1	< 0.001
PWT (mm)	0.80 ± 0.13	0.87 ± 0.12	0.96 ± 0.1	< 0.001
LV mass index (g/m ²)	67.6 ± 12.2	76.7 ± 14.1	81.2 ± 15.1	0.005
E/A ratio	1.34 ± 0.19	1.11 ± 0.25	1.09 ± 0.21	< 0.001
E/Em ratio	6.1 ± 1.5	7.3 ± 1.3	8.2 ± 1.5	< 0.001

LV: Left ventricular, EDD: End-diastolic diameter, ESD: End-systolic diameter, IVS: Interventricular septum, PWT: Posterior wall thickness, EF: Ejection fraction, E/A: Early diastolic and atrial velocity ratio, E/Em: Ratio of peak early mitral inflow velocity and peak early diastolic mitral annular velocity.

Alcoholic patients had consumed a mean daily dose of ethanol of 185 ± 44 g (range 95-320 g) over a period of 13.9 ± 4.3 years (range 6-27 years), with a mean TLDE of 13.2 ± 4.2 kg ethanol/kg body weight (3.9-20.2 kg/kg). There was a significant difference in the duration of drinking among the alcoholic groups ($p \leq 0.001$). Also, daily ethanol consumption showed that there was a significant difference between groups I and II ($p = 0.002$).

Among alcoholic patients, group I included 6 (14%) and group II included 8 (25%) hypertensive patients. There was a slight difference between groups in terms of having hypertension ($p = 0.04$).

Conventional Echocardiographic Measurements

The left ventricular functional parameters are shown in Table 2. EF did not differ between the healthy controls and alcoholic patients. Although the LV dimensions such as end-diastolic diameter (EDD) and end-systolic diameter (ESD) and LV mass index were higher in alcoholic patients compared to the controls, these parameters were comparable among the alcoholic groups. Post hoc analyses revealed that for EDD, healthy controls vs. group I, $p = 0.03$, healthy controls vs. group II, $p = 0.004$, for ESD, healthy controls vs. group I, $p = 0.04$ and healthy controls vs. group II, $p = 0.008$ and for LV

Table 3. Left Centricular strain and strain rate measurements of healthy controls and alcoholic patients

Variables	Healthy controls n= 30	Alcoholic patients n= 75		p value
		Grup I n= 43	Group II n= 32	
G-LS (%)	-19.9 ± 2.7	-18.3 ± 1.6	-17.0 ± 1.5	< 0.001
G-SRsys (s ⁻¹)	-1.2 ± 0.5	-1.0 ± 0.1	-0.9 ± 0.1	0.03
G-SRearly (s ⁻¹)	1.2 ± 0.2	1.2 ± 0.1	1.2 ± 0.2	NS
G-SRlate (s ⁻¹)	0.9 ± 0.1	0.8 ± 0.3	0.9 ± 0.2	NS

G-LS: Global longitudinal strain, G-SRsys: Global systolic strain rate, G-SRearly: Global diastolic strain rate during the early phase of diastole, G-SRlate: Global diastolic strain rate during the late phase of diastole.

mass index, healthy controls vs. group I, p= 0.05 and healthy controls vs. group II, p= 0.004. There were no differences in EDD, ESD and LV mass index among the alcoholic groups. The left ventricular PW and IVS were thicker in the alcoholic groups. Post hoc analysis showed that for IVS, healthy controls vs. group I, p= 0.01, healthy controls vs. group II, p≤ 0.001 and group I vs. group II, p= 0.03 and for PW thickness, healthy controls vs. group I, p= 0.05, healthy controls vs. group II, p≤ 0.001 and group I vs. group II, p= 0.04.

The Doppler-derived variables, E/A ratio and E/Em showed differences between the controls and alcoholic patients. However, there were no differences in these parameters among the alcoholic groups.

LV deformation Analysis

The 2D global longitudinal systolic strain (G-LS) appeared significantly lower in alcoholic patients in comparison with that in the controls (p≤ 0.001). G-LS was found to significantly differ between the healthy controls and alcoholic groups (i.e. group I and group II) (Figure 2).

Although G-SRsys was lower in the alcoholic groups than that in the control group (p= 0.03), there were no differences in G-SRearly and G-SRlate values (Table 3).

To demonstrate the effect of TLDE on echocardiographic abnormalities, we assessed the correlation analysis, which showed a significant positive moderate correlation of G-LS values with TLDE (r= 0.49, p< 0.001) (Figure 3).

DISCUSSION

The main finding of our study was the demonstration of LV systolic abnormalities by 2D-STE in chronic alcoholic patients. This cross-sectional study is the first work to demonstrate subclinical LV dysfunction in chronic asymptomatic alcoholic patients using the 2D-STE method. This novel method allowed us to detect early LV systolic dysfunction in chronic alcoholic patients, and the LV-EF results did not differ from those of the healthy controls. Moreover, although there were no differences in LV dimensions (EDD and ESD) and the LV mass index among the alcoholic groups, there was a significant difference in G-LS. In addition, a significant correlation was found between TLDE and G-LS.

Alcohol leads to structural and functional changes in the

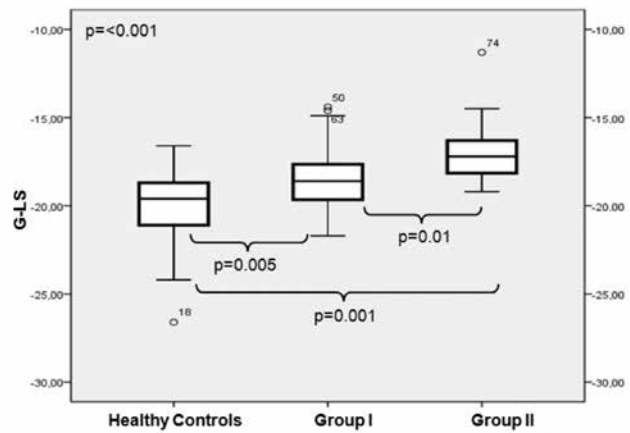


Figure 2. The box-plot graphic displays the difference in the global longitudinal systolic strain (G-LS) between healthy controls and the alcoholic groups I and II.

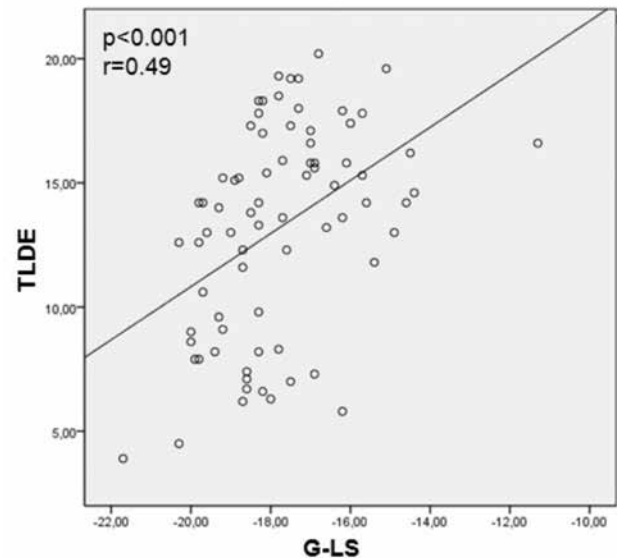


Figure 3. Correlation between the global longitudinal systolic strain (G-LS) and total lifetime dose of ethanol (TLDE).

myocardium. It has a negative impact of cardiac myofibril shortening and on the composition of myoproteins⁽⁷⁾. Although there is a lack of consensus, it was shown that alcoholic patients had detectable changes in cardiac structure and function in cases with said patients consuming > 90 g/day of alcohol for ≥ 5 years⁽⁸⁻¹⁰⁾.

Recently, the development of 2D-STE, a technique that is independent of the ultrasound angle of interrogation, has facilitated the subtle early detection of LV systolic dysfunction (depressed longitudinal deformation) in heart disorder patients without an altered EF⁽³⁾. Identifying subclinical LV systolic dysfunction among chronic alcoholic patients might be helpful in identifying patients at higher risk of heart failure.

Several studies have investigated the role of alcohol in determining abnormalities of LV size and function. These studies have been addressed to find the relationship of LV function with the parameters of ethanol consumption using 2D and M-mode echocardiography. However, the results are conflicting. These discrepancies may result from the wide variations in diagnostic criteria and age and the use of different parameters for ethanol consumptions, e.g. daily intake, duration of alcoholism and TLDE.

Askanas et al. found no difference in LV mass or systolic function between alcoholic patients with a drinking history longer than 15 years and those with a history shorter than 15 years⁽¹¹⁾. However, they did not take into consideration the quantity of daily consumption.

Kino et al. examined 22 alcoholic patients who consumed more than 125 mL/day and 12 alcoholic patients who consumed less⁽¹²⁾. They did not find differences in LV size, mass or function between two groups. However, the duration of alcoholism was neglected.

Dancy et al. used M-mode echocardiography and found that chronic alcohol abuse is an important independent risk factor for cardiac dilatation and that an increase in EDD may be an early marker of alcoholic cardiomyopathy⁽¹³⁾.

Kupari et al. reported that no relation could be found between the duration and quantity of alcohol abuse and LV hypertrophy and dysfunction⁽⁹⁾. However, they found LV hypertrophy and mild systolic dysfunction in alcoholic patients. Nevertheless, another study from the same group revealed no significant abnormalities in LV systolic function as assessed by echocardiography (as evaluated by the fractional shortening percentage) in chronic alcoholics⁽¹⁴⁾.

Lazarevic et al. used conventional echocardiographic methods to evaluate the cardiac structure and function in healthy controls and in those with chronic alcohol consumption (alcohol consumption > 90 g/day and ≥ 4 day/week). They composed three different groups based on the duration of heavy drinking (group S, drinking history of 5-9 years, group I, drinking history of 10-15 years and group L, drinking history of > 15 years). All alcoholic patients were asymptomatic for cardiovascular disease. They found that the LV dimensions, end-diastolic dimension (EDD) and end-systolic dimension (ESD) were increased in group S. In group I, although no further

increases were found in the LV dimensions and LV myocardial mass index, the PW and IVS thickness were significantly increased. In group L and group I, these parameters were comparable. Comparing alcoholic patients to healthy controls showed that asymptomatic alcoholic patients had slightly dilated ventricles with normal EF. They concluded that LV dilation is an early finding that precedes an increase in LV mass. Additionally, the duration of drinking did not influence the ventricular volume or EF.

The presented study showed similar findings to this study. It appears that in asymptomatic male alcoholic patients, the most prominent early findings were an increase in the interventricular septal and posterior wall thickness and LV dimensions (EDD and ESD) as well as an increase in LV mass. However, while we did not find the difference between EF and TLDE, we were able to see the difference with a novel echocardiographic method, namely 2D-STE. Using a speckle-tracking derived strain and newer angle-independent echocardiographic method, we found that chronic alcoholic patients have a reduced longitudinal left ventricular systolic function, despite still having a normal ejection fraction. Interestingly, we showed there was a correlation between the TLDE and the degree of LV dysfunction in chronic alcoholics.

Although, some studies showed that the duration and amount of alcohol consumed by asymptomatic alcoholic patients does not correlate with changes in the myocardial structure and function^(8,11,14-16), Urbano-Marquez et al. found that the total lifetime dose of alcohol (20 kg/kg bodyweight) was correlated to an increase in LV mass and a decrease in ejection fraction⁽¹⁷⁾. In their study, however, only a minority of the study population (mean duration of drinking, 16.2 years) had a lower EF. Although we used TLDE for classification, EF did not differ between the groups. A possible reason for this discrepancy could be differences in the severity of alcoholism. They included a longer duration of drinking in their study population than in our study group. Additionally, in the present study, TLDE was in the range of 3.9 to 20.2 (mean, 13.2 kg/kg), which is lower than in the aforementioned study.

In the current study, we compared alcoholic patients based on the TLDE status. We believe that in light of the existing data, since TLDE involves the quantity of daily consumption as well as the duration of alcohol consumption, it is the more appropriate classification criteria than either the dose or duration.

In fact, hypertension and other cardiovascular disease, such as atrial fibrillation and heart failure, are affected by heavy alcohol consumption. Moreover, it is possible that these comorbidities may predispose alcoholic patients to changes in the myocardial structure or function. Thus, it is important to emphasize that studies should be adjusted for other potential determinants of the LV measurements, such as age, obesity, blood pressure and smoking status. However, most studies have ignored these determinants. In the presented study, some of alcoholic patients had concomitant hypertension, which also affects longitudinal function. To adjust the analyses for other potential determinants of the LV measurements,

analysis of covariance was used, which models covariates to statistically control for baseline differences in variables. In a study conducted by Lazarevic et al., who investigated preclinical cardiac abnormalities in chronic alcoholic patients, they excluded patients with a history of hypertension at the beginning of the study⁽⁸⁾. Although even with this exclusion criterion, hypertension was observed during hospital stay in 16 (52%) patients with a drinking history of 5-9 years, in 16 (52%) patients with a drinking history of 10-15 years and in 16 (59%) patients with a drinking history of more than 15 years. Thus, the exclusion of hypertensive or smoker alcoholic patients would produce a significant bias in our results. Similarly, Kupari and Koskinen found an inverse relation of LV function (determined by fractional shortening) to alcohol use⁽¹⁸⁾. Also, the reduction in LV function with alcohol cannot be explained by covariates, such as blood pressure, smoking and physical activity, which can all influence LV measurements⁽¹³⁾.

Alcoholic patients were considered to have a low probability of coronary artery disease based on clinical examination, a normal treadmill exercise test and normal resting echocardiography. Coronary angiography was not performed in patients, because it was not clinically indicated.

Interestingly, age is not a variable, since in all of the studies reviewed, the mean age of the asymptomatic male subjects ranged from 38.5 to 44 years⁽¹⁵⁾. The presented study showed similar findings, with a mean age of 39.5 ± 6.5 years.

Study Limitations

Our study size was relatively small. However, the accurate selection of never-treated for alcoholism and the inclusion of highly selected patients (asymptomatic, without a history of angina and/or myocardial infarction and/or normal EF) can justify the small number. Although the study sample is small, it is consistent with the criteria for a homogeneous population. As only male subjects were included in our study, the effects of alcoholism on LV systolic function in women were not assessed. Second, since there are no data related to the classification, we grouped patients into two groups according to TLDE, which should be useful to assess the effects of alcohol intake on LV structure and LV function, as assessed by 2D-STE. Another limitation is that this is a cross-sectional study. Further longitudinal investigations are needed to better clarify these preliminary findings on the basis of a larger population. Although the history of alcohol intake was obtained from their families and friends as well as from patients, the exact information on the quantities of alcohol consumption may still be underestimated by alcoholic patients.

CONCLUSIONS

To the best of our knowledge, this is the first study demonstrating the presence of early functional abnormalities of longitudinal systolic function by 2D-STE in chronic alcoholic patients. These functional mechanics have a parallel impairment with the increase in alcohol consumption.

CONFLICT of INTEREST

There is no conflict of interest to declare in this study.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: AK, CYK, VO, GK

Analysis/Interpretation: AK, CYK, TA, AE, CK

Data Acquisition: AK, GK, CYK, AE, RB, AG

Writing: AK, CYK, GK

Critical Revision: AK, CYK, VO, AI

Final Approval: All of authors

REFERENCES

1. Regan TJ. Alcohol and the cardiovascular system. *JAMA* 1990;264:377-81.
2. Iacovoni A, De Maria R, Gavazzi A. Alcoholic cardiomyopathy. *J Cardiovasc Med (Hagerstown)* 2010;11:884-92.
3. Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. *J Am Coll Cardiol* 2006;47:789-93.
4. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused update incorporated in to the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol* 2009; 53:1-90.
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders- DMS-V*. 5th ed. Washington, DC: American Psychiatric Association, 2013.
6. Vittadini G, Buonocore M, Colli G, Terzi M, Fonte R, Biscaldi G. Alcoholic polyneuropathy: a clinical and epidemiological study. *Alcohol and Alcoholism* 2001;36:393-400.
7. Delbridge LM, Connell PJ, Harris PJ, Morgan TO. Ethanol effects on cardiomyocyte contractility. *Clin Sci (Lond)* 2000;98:401-7.
8. Lazarević AM, Nakatani S, Nesković AN, Marinković J, Yasumura Y, Stojčić D, et al. Early changes in left ventricular function in chronic asymptomatic alcoholics: relation to the duration of heavy drinking. *J Am Coll Cardiol* 2000;35:1599-606.
9. Kupari M, Koskinen P, Suokas A. Left ventricular size, mass and function in relation to the duration and quantity of heavy drinking in alcoholics. *Am J Cardiol* 1991;67:274-9.
10. George A, Figueredo VM. Alcoholic cardiomyopathy: a review. *J Card Fail* 2011; 17:844-9.
11. Askanas A, Udoshi M, Sadjadi SA. The heart in chronic alcoholism: a noninvasive study. *Am Heart J* 1980;99:9-16.
12. Kino M, Imamitchi H, Moriguchi M, Kawamura K, Takatsu T. Cardiovascular status in asymptomatic alcoholics, with reference to the level of ethanol consumption. *Br Heart J* 1981;46:545-51.
13. Dancy M, Bland JM, Leech G, Gaitonde MK, Maxwell JD. Preclinical left ventricular abnormalities in alcoholics are independent of nutritional status, cirrhosis, and cigarette smoking. *Lancet* 1985;1:1122-5.
14. Kupari M, Koskinen P, Suokas A, Ventilä M. Left ventricular filling impairment in asymptomatic chronic alcoholics. *Am J Cardiol* 1990; 66:1473-7.
15. Piano MR. Alcoholic cardiomyopathy: incidence, clinical characteristics, and pathophysiology. *Chest* 2002;121:1638-50.
16. Mathews EC Jr, Gardin JM, Henry WL, Del Negro AA, Fletcher RD, Snow JA, et al. Echocardiographic abnormalities in chronic alcoholics with and without over congestive heart failure. *Am J Cardiol* 1981;47:570-8.
17. Urbano-Marquez A, Estruch R, Navarro-Lopez F, Grau JM, Mont L, Rubin E. The effects of alcoholism on skeletal and cardiac muscle. *N Engl J Med* 1989; 320:409-15.
18. Kupari M, Koskinen P. Relation of left ventricular function to habitual alcohol consumption. *Am J Cardiol* 1993; 72:1418-24.