Subclinical Myocardial Dysfunction Revealed by Two-dimensional Speckle Tracking Echocardiography in Chronic Alcoholic Patients

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Research

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Abstract

Background and aim:

Alcohol is a potent risk factor for heart diseases. Alcohol consumption can damage myocytes earlier than overt LV dysfunction occurs. We aimed that two-dimensional speckle tracking echocardiography (2DSTE) can be used for early detection of heart failure caused by alcohol intake.

Methods:

A 100 chronic alcoholics were enrolled into the study. All patients underwent physical examination, biochemical analysis and echocardiography. Following parameters were assessed: LV diameters, LV systolic and diastolic function. Also RV diameters, LA and RA volumes were measured. LV and RV global longitudinal strain (GLS), LA and RA strain were calculated. The results were compared with control group, composed of 20 healthy subjects.

Results:

The mean LVEF was $57.55 \pm 6.99\%$, the mean E/A ratio 1.09 ± 0.32 and $E/E' 7.36 \pm 2.4$ in the study group. Mean LA volume was 35.4 ± 10.78 mL, RA volume 34.7 ± 10.25 mL. The 2DSTE of LA was 29.1 ± 10.0 , LVGLS was -15.03 ± 2.07 . The RA strain was 30.46 ± 10.25 and RVGLS -16.22 ± 6.27 . All strain parameters were lower than in the control group. Graded reduction of global longitudinal strain of the both ventricles and both atria in dose-dependent manner was found, lower strain was observed in heavy alcoholics than light/moderate drinkers.

Conclusions:

The study proved that chronic alcohol consumption leads to myocardial injury in dose-dependent manner, the deterioration of global strain of the ventricles and atria can be the sensitive marker of myocardial injury.

Introduction

Alcohol is a potent risk factor for heart diseases; chronic excessive alcohol consumption leads to the damage of its structure and function [1, 2].

An extreme form of toxic effects on heart caused by ethanol is alcoholic cardiomyopathy, which is observed in about 10% of alcoholics with the prevalence range of 23–40% [3]. Conventional transthoracic echocardiography can detect reduced left ventricle ejection fraction (LVEF), left ventricle (LV) dilatation, left ventricular hypertrophy, diastolic dysfunction, enlargement of the left (LA) and right (RA) atrium or impaired right ventricle (RV) function.

It is believed that alcohol consumption can damage myocytes and cause fibrosis much earlier than the left ventricle systolic dysfunction occurs [4]. It has been proved that moderate doses of ethanol are associated with incident atrial fibrillation [5]. Early alcohol withdrawal may improve LV function, thus predicting cardiotoxicity caused by alcohol intake at an early stage may improve the prognosis in patients with high risk of developing cardiomyopathy [6]. Thus, it is highly important to find the markers of early, subclinical myocardial dysfunction before the development of an overt dysfunction. Two-dimensional speckle tracking echocardiography (2DSTE) is an early, sensitive and objective marker of myocardial dysfunction and can also be useful in early diagnosis and prognosis of an injury caused by alcohol abuse [7].

Our study aims to detect the preclinical functional cardiac abnormalities using two-dimensional speckle tracking echocardiography in clinically asymptomatic alcoholics. We hypothesized that the 2DSTE enables finding the subclinical abnormalities of heart function and may be helpful in finding the relationship between the parameters describing myocardial dysfunction and the data describing alcohol dependence.

Patients And Methods

Study group

A 100 of consecutive patients with documented alcohol abuse, who were a part of the inpatient alcohol dependence program in the Department of Psychiatry, Cracow, Poland between September 2018 and November 2019 were enrolled into the study. The following entry criteria were established: 1. alcohol abuse diagnosed; patients were treated in the Alcohol Dependency Treatment Ward with diagnosis of alcohol addiction (according to ICD 10 codes: F10.2, F10.3, F10.4) 2. no signs of cardiac, respiratory or metabolic diseases 3. adequate visualisation of heart structures 4. no atrial fibrillation at the time of assessment due to the inability to perform accurate speckle tracking calculations.

We used a standardized questionnaire to collect the patients demographic data,

the information about cardiovascular risk factors and the information about the total duration of alcohol consumption, the amount of alcohol they usually consumed per day and the duration of the abstinence periods and drinking binges.

The control group was composed of twenty healthy subjects without drinking history. None of the patients in the control group had history of cardiovascular, respiratory or metabolic diseases.

Clinical and laboratory evaluation

All patients underwent a detailed physical examination and a biochemical analysis. The anthropometric assessment of height and weight was measured, as well as the body mass index (BMI, kg/m²) and body surface area (BSA, m²) were calculated. The blood pressure was measured after a 10-minute rest. The

biochemical parameters (total cholesterol, low density cholesterol (LDL), high density cholesterol (HDL), triglycerides, NT-proBNP) were assessed.

Echocardiography

The comprehensive echocardiographic examinations were performed in 100 alcoholics and 20 matched controls.

All the echocardiographic measurements were uniformly performed by a single, trained cardiologist during the entire recruitment period using Philips EPIQ 7C ultrasound machine equipped with the S5-1 probe (3.5 MHz transducer). The echocardiographic loops were obtained in the supine position and in the left lateral decubitus position at the end of normal breath with the frame rate of 40–80 frames/second. At least three consecutive loops were recorded for each analysis.

Standard echocardiographic evaluation

The protocol of standard echocardiography included measurements of the LV end systolic (LVESD) and the LV end diastolic diameters (LVEDD), the LA and RA volumes using biplane Simpson method. The LV ejection fraction was measured as a maximal volume – minimal volume/maximal volume x 100. The LV diastolic function was measured as a pulsed wave Doppler as early (E) and late (A) diastolic LV filling velocities at the tip of the mitral leaflets from the apical four chamber view. The average septal and lateral relaxation velocity (E

) was assessed using $gDopp \leq rtissueimag \in g(TDI) \rightarrow estimate \frac{E}{E}$ ratio. The right ventricle was measured in apical four-chamber view in the basal (RVD1) and the middle (RVD2) part of the cavity.

Two-dimensional speckle-tracking analysis protocol

The LV deformation was assessed using two-dimensional images from the three LV apical views (A4C) for longitudinal strain (3-chamber, 2-chamber and apical four-chamber axis views), the mean frame rate was set to 60–80 frames/second. The baseline two-dimensional images were analysed off-line using an automatic endocardial border tracing by a dedicated software. If the software was not able to detect a given segment due to a poor image quality, the endocardial border was marked manually. The aortic valve closure was detected automatically through ECG gating. In order to analyse the LA and the RA strain, the LA and RA endocardial borders were manually traced in A4C views, thus delineating a region of interest (ROI). After visually verifying the quality of tracings and the possible manual adjustment of the ROI, the software automatically calculated and generated time-longitudinal strain curves. The RV global longitudinal strain was calculated from apical four chamber view from the free wall of the right ventricle, the RV endocardial border was traced manually and then the software would automatically calculate the global result.

The strain results were compared with the standard reference values [7, 8, 9]. Results of the deformation were analysed in groups due to quantity of consumed alcohol (group A – one to five drinks daily, group B

– more than five drinks daily) and the duration of alcohol abuse (group C – time alcohol abuse < 5 years, group D – time of alcohol abuse > 5 years).

Statistical analysis

Continuous and categorical variables was expressed as means $\pm$ standard deviation (SD) and percentages. Correlations were analysed using Spearman's test. Test t was used to compare continuous variables. ANOVA test was used to compare two alcoholic groups and the control group (analysis of the three groups). A *p* value of less than 0.05 was regarded as significant for all the analyses. All statistical tests were performed with Statistica 13.1 software.

Ethics approval and consent to participate

The study followed the principles of the Declaration of Helsinki. All procedures involving human participants were performed in accordance with the ethical standards of the institutional and national research committee. The study protocol was approved by the local ethics committee. Written consent was obtained from all patients before being enrolled in the study.

Table 1
Daily alcohol consumption.

	Portion of consumed alcohol	Number of patients
1.	0–2 drinks	2
2.	3–5 drinks	6
3.	6–10 drinks	14
4.	11–20 drinks	27
5.	More than 20 drinks	51

Table 2
Duration of alcohol abuse.

	Time of alcohol abuse	Number of patients
1.	Less than 1 year	12
2.	1–5 years	28
3.	5–10 years	24
4.	More than 10 years	17
5.	More than 20 years	18
6.	No data	1

Table 3
Duration of drinking binge.

	Duration of alcohol binge	Number of patients
1.	< 3 days	13
2.	3–7 days	24
3.	< 1 month	26
4.	> 1 month	22
5.	Every day drinking	14
6.	No data	1

Table 4
Myocardial GLS results graded by alcohol consumption.

GLS	Group A (N = 8)	Group B (N = 92)	Control (N = 20)	p for ANOVA
LV	-14.89 ± 3.17	- 15.04 ± 1.97	-20.31 ± 2.04	p = 0,000
LA	25.65 ± 8,72	29.28 ± 10.11	37.51 ± 11.55	p = 0,0055
RV	-17.94 ± 5.86	- 16.07 ± 6.31	-23.245 ± 2.57	P = 0,000
RA	26.05 ± 13.45	30.85 ± 9.93	41.065 ± 12.37	p = 0,0002
GLS, global longitudinal strain; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle				

Table 5
Myocardial GLS results graded by time of alcohol abuse (alcohol binge).

GLS	Group C (n = 40)	Group D (n = 60)	Control (n = 20)	p for ANOVA
LV	-15.40 ± 2.13	-14.82 ± 2.07	-20.31 ± 2.04	p = 0,00
LA	28.99 ± 10.25	26.94 ± 10.11	37.51 ± 11.55	p =,0002
RV	- 16.22 ± 6.27	- 15.37 ± 6.31	-23.245 ± 2.57	p = 0,00
RA	30.46 ± 10.86	30.93 ± 10.31	41.065 ± 12.37	p = 0,0004
GLS, global longitudinal strain; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle				

Results

Baseline demographics

The study group consisted of 100 asymptomatic patients with chronic alcohol abuse in the mean age 44.13 ± 9.85 (range 25-73) years hospitalised in the Alcohol Dependency Treatment Ward from

September 2018 to November 2019. 21 women and 79 men were enrolled, the mean BMI was 18.9 ± 3.91 (range 16.9 – 35.0) kg/m². Patients used to consume from 2 to more than 20 portions of alcohol daily (tab.1.). The duration of alcohol drinking was from less than one year to more than 20 years (tab.2.). 25% of patients were on detoxification before their enrolment to the study, 35% were on the therapy more than 2 times. The duration of drinking binges is shown in tab.3. Mean abstinence time was 30.47 ± 39.42 (range 0-180) months.

In the laboratory tests the mean LDL cholesterol level was 3.56 ± 0.98 (2.01 – 6.71) mmol/l, HDL 1.19 ± 0.33 (0.52 – 2.56) mmol/l, the triglycerides level was 2.46 ± 1.38 (0.64 – 8.54) mmol/L and NTproBNP level 63.34 ± 53.28 (5 – 292) mmol/l. The mean systolic blood pressure was 138.14 ± 12.42 (110-160) mmHg, diastolic 83.00 ± 9.87 (67 – 102) mmHg.

The control group was composed of 20 patients (11 women, 9 men) with no history of alcohol abuse in the mean age 41.26 ± 8.75 (range 24-62) years.

Conventional echocardiographic measurements

The mean LVEF in the study group was $57.55 \pm 6.99\%$. The LV dimensions: LVEDD and LVESD diameters were in normal limits (LVEDD 49.47 ± 3.71 mm; LVESD 31.97 ± 4.76 mm). Doppler-derived variables were as follows: the mean E/A ratio was 1.09 ± 0.32 and E/E' 7.36 ± 2.4 . The mean LA volume was 35.4 ± 10.78 mL, the RA volume 34.7 ± 10.25 mL. The dimensions of RV ventricle were: RVD1 32.55 ± 3.5 mm and RVD2 22.65 ± 3.68 mm.

The mean LVEF in the control group was $65.85 \pm 4.0\%$. The LV dimensions were: LVEDD 46.5 ± 2.65 mm; LVESD 29.35 ± 2.48 mm. Mean E/A ratio was 1.19 ± 0.26 and E/E' 5.85 ± 1.21 . Dimensions of RV ventricle were RVD1 21 ± 2.66 mm and RVD2 22.45 ± 3.03 mm.

The LVEF was significantly higher in the control group ($p=0.007$), but there was no significant difference between other parameters in both groups.

LV deformation analysis

In the study group the two-dimensional strain of the LA was 29.1 ± 10.0 , the LV global longitudinal strain was -15.03 ± 2.07 . The RA global strain was calculated as 30.46 ± 10.25 and the RV global longitudinal strain -16.22 ± 6.27 .

In the control group the two-dimensional strain of the LA was 37.51 ± 11.55 , LV global longitudinal strain was -20.31 ± 2.04 . RA global strain was calculated as 41.065 ± 12.37 and RV global longitudinal strain -23.245 ± 2.57 . All the obtained strain parameters were significantly lower in the study group comparing to the reference values and the control group.

The significant reduction of global longitudinal strain of the LV, RV, LA and RA was observed in study group comparing to the control group (tab.4.). Across the categories of increasing alcohol consumption

from group A to B, we found graded reduction of GLS across ordered alcohol intake categories; light/moderate (group A) and heavy (group B) drinkers had lower GLS parameters comparing to the control group; also strain parameters were significantly reduced in heavy drinkers in comparison to light/moderate drinkers.

Also there was a graded, significant reduction of GLS across categories based on duration of alcohol binges. In group D (drinking by alcohol binges longer than 5 years) global longitudinal strain was significantly lower than in group C (drinking by alcohol binges from 1 to 4 years), $p < 0,05$. In both groups GLS was significantly lower than in control group (tab.5.).

Discussion

Excessive, long-term alcohol consumption leads to functional and structural changes in the myocardium. These changes include myocyte death, intracellular dysfunction and the deterioration of mitochondrial structure and sarcoplasmic reticulum [10]. Also, it has been shown that the cardiac myofibril shortening, the composition of contractile proteins and calcium homeostasis were disturbed by chronic alcohol use [11]. These pathological changes may lead to alcoholic cardiomyopathy.

The main purpose of the study was to demonstrate early systolic abnormalities of the left and the right ventricle among the chronic alcoholic patients.

It was already shown that despite the normal LVEF, the subclinical systolic LV dysfunction measured by 2DSTE can occur among the alcoholics [4]. Chronic alcohol abuse leads also to the deterioration of the RV function [12].

Abstaining from alcohol can lead to the improvement of myocyte function and the increase in ejection fraction of the left ventricle [6,13]. 2DSTE can show subtle subclinical cardiac changes despite preserved ejection fraction [14,15,16,17,18,19]. In the presented study global longitudinal strain of left ventricle was also significantly lower comparing to the control group and reference values despite normal ejection fraction of the LV.

In several studies the correlation between alcohol consumption and LV function was analysed, but the results were conflicting and inconsistent [4,20].

In previously published observations it was shown that consuming more than 90 g of alcohol/day for more than 5 years can cause detectable changes in the cardiac structure [21,22,23]. It has been supposed that the duration of alcohol consumption is more important than the quantity of the daily alcohol consumption in developing heart failure [24,25].

A small study showed no difference in the LV size and function in two alcoholic groups: drinking more and less than 125 mL/day [26]. Kupari and al. published that diastolic dysfunction is an early abnormality in asymptomatic alcoholics with median 11 years duration of alcohol abuse, but found no relation between quantity and duration of the alcohol consumption and echocardiographic parameters

describing the LV function [27]. Likewise, Silberbauer et al. found no correlation between the LV diastolic dysfunction and the duration and amount of chronic alcohol intake [16]. Cerqueira et al. showed no differences in the LV diastolic dysfunction and chronic alcohol abuse, but in another study Fernandez-Sola et al. found a strong correlation between alcohol consumption and the decrease of the E/A index in dose-dependent manner [18,28]. In the presented study no significant correlation was found between diastolic dysfunction and amount and time of alcohol abuse.

Lazarevic et al. compared three group of alcoholics based on the duration of alcohol abuse and found that asymptomatic alcoholics had slightly dilated ventricles with a normal LVEF, but the duration of alcohol dependency was not correlated with the LV diameters, volume or function [29]. Urban et al. proved that the total lifetime dose of alcohol (20 kg/body weight) was correlated with increased LV mass and a decreased LVEF [30]. Kalayci et al. found in a small study that lower GLS correlates with the total lifetime of alcohol intake [31].

In our study we found that LV GLS was significantly lower in the study group than in the control group. Reduction of LV GLS was correlated with amount of used alcohol in dose-dependent manner, patients drinking more than 5 drinks daily had significantly lower LV GLS than patients using less than 5 drinks daily. It was also showed, that heavy alcohol abuse (duration of drinking binges more than 5 years) leads to greater impairment of LV GLS than moderate drinking (duration of drinking binges from 1 to 5 years).

Chronic alcohol consumption can lead not only to deterioration of the LV function, but also it can cause functional abnormalities of the RV; significant reduction of the RV global longitudinal strain was observed among chronic asymptomatic alcoholics. In the presented study we observed, that RV GLS was significantly lower in the heavy drinkers comparing to moderate drinkers. Lower RV GLS value was reduced in dose dependent manner, in patients drinking more than 5 drinks daily RV dysfunction was more marked than in moderate drinkers (1-5 drinks daily).

Light to moderate chronic alcohol consumption can cause subtle LA functional abnormalities comparing to nondrinkers and may predispose to incident AF [32]. There is no published data concerning the RA dysfunction in chronic alcoholic patients so far. In the study global strain of the left atrium and the right atrium were significantly decreased in the active group comparing to the controls. Likewise LV and RV GLS, global longitudinal strain of both atria was correlated with amount of alcohol used daily and time of alcohol binges.

Study Limitations

The main limitation of our study is a relatively small study group, which was composed mainly of men. It is difficult to extrapolate the results for women and the effect of chronic alcohol consumption on cardiac structure and function among women cannot be assessed. The data concerning alcohol abuse and the history of alcoholism was based on the questionnaires completed only by the patients, therefore the information about alcohol consumption could have been underestimated. A continuation of the study should be performed to assess chronic alcohol abuse on cardiac function.

Conclusions

In the presented study we observed that chronic alcohol consumption leads to the myocardial injury in the dose-dependent manner; global longitudinal strain is a sensitive marker of the myocardial dysfunction. Lower global longitudinal strain was observed in heavy drinkers, but even light to moderate doses are associated with significantly reduced cardiac mechanics.

Declarations

All procedures involving human participants were performed in accordance with the ethical standards of the institutional and national research committee. The study protocol was approved by the local ethics committee. Written consent was obtained from all patients before being enrolled in the study.

This manuscript has not been previously published and is not under consideration in the same or substantially similar form in any other peer-reviewed media.

The data that supports the findings of the study are available within the article and its supplementary material.

All authors listed have contributed sufficiently to the project to be included as authors; all authors have reviewed the article and agree with its contents.

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To the best of our knowledge there is no conflict of interest.

All authors give consent for publication in case the manuscript is accepted.

References

1. Guo R, Ren J. Alcohol and acetaldehyde in public health: from marvel to menace. *Int J Environ Res Public Health* 2010;7:1285-1301.
2. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 2009;373:2223-2233.
3. George A, Figueredo V. M. Alcoholic cardiomyopathy: a review. *Journal of Cardiac Failure*. 2011;17(10):844–849. doi: 10.1016/j.cardfail.2011.05.008.
4. Kucuk M, Oncel C.R, Yildirim A, Canan F, Kuloglu M.M. Evaluation of subclinical left ventricular systolic dysfunction in chronic asymptomatic alcoholics by speckle tracking echocardiography. *Biomed Res Int*. 2017;2017:6582568. doi: 10.1155/2017/6582568.
5. Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. *J Am Coll Cardiol* 2014;64:281-289.

6. Guillo P, Mansourati J, Maheu B. et al. Long-term prognosis in patients with alcoholic cardiomyopathy and severe heart failure after total abstinence. *American Journal of Cardiology*. 1997;79(9):1276–1278. doi: 10.1016/S0002-9149(97)00101-X.
7. Badano L.P, Kolas T.J, Muraru D et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging*. 2018 Jun 1;19(6):591-600. doi: 10.1093/ehjci/jey042.
8. Lang R.M, Badano L.P, Mor-Avi V et.al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28 (1):1–39.e14.
9. Voigt J.U, Pedrizzetti G, Lysyansky P, Marwick T.H et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16 (1):1–11.
10. Holmes M, Dale C, Zuccolo et.al. Association between alcohol and cardiovascular disease mendelian randomisation analysis based on individual participant data *BMJ*, 2014; 349 doi: <https://doi.org/10.1136/bmj.g4164>
11. Laonigro I, Correale M, Di Biase M, Altomare E. Alcohol abuse and heart failure. *European Journal of Heart Failure*. 2009;11(5):453–462. doi: 10.1093/eurjhf/hfp037.
12. Meng S, Guo L, Li G. Early changes in right ventricular longitudinal function in chronic asymptomatic alcoholics revealed by two dimensional echocardiography. *Cardiovasc Ultrasound*. 2016; 14: 16. doi: [10.1186/s12947-016-0058-3](https://doi.org/10.1186/s12947-016-0058-3)
13. Demakis J. G, Proskey A, Rahimtoola S.H et al. The natural course of alcoholic cardiomyopathy. *Annals of Internal Medicine*. 1974;80(3):293–297. doi: 10.7326/0003-4819-80-3-293.
14. Prazak P, Pfisterer M, Osswald S, Buser P, Burkart F. Differences of disease progression in congestive heart failure due to alcoholic as compared to idiopathic dilated cardiomyopathy. *European Heart Journal*. 1996;17(2):251–257.
15. Doi: 10.1093/oxfordjournals.eurheartj.a014842.
16. Mahmoud S, Beauchesne L.M, Davis D.R, Glover C. Acute reversible left ventricular dysfunction secondary to alcohol. *Canadian Journal of Cardiology*. 2007;23:475–477.
17. Silberbauer K, Juhasz M, Ohrenberger G, Hess C. Noninvasive assessment of left ventricular diastolic function by pulsed doppler echocardiography in young alcoholics. *Cardiology*. 1988;75(6):431–439. doi: 10.1159/000174413.
18. Friedman H.S, Vasavada B.C, Malec A. M, Hassan K.K, Shah A, Siddiqui S. Cardiac function in alcohol-associated systemic hypertension. *The American Journal of Cardiology*. 1986;57(4):227–231. doi: 10.1016/0002-9149(86)90896-9.
19. Cerqueira M.D, Harp G.D, Ritchie J.L, Stratton J.R, Walker R.D. Rarity of preclinical alcoholic cardiomyopathy in chronic alcoholics <40 years of age. *The American Journal of Cardiology*. 1991;67(2):183–187. doi: 10.1016/0002-9149(91)90442-n.

20. Askanas A, Udoshi M, Sadjadi S.A. The heart in chronic alcoholism: a noninvasive study. *American Heart Journal*. 1980;99(1):9–16. doi: 10.1016/0002-8703(80)90309-9.
21. Kocabay G, Karabay C, Kalayci , Oduncu V, Akgun T, Guler A, Kılıçgedik A, Kalkan S, İzgi A, Kirma C. Left atrial function by speckle-tracking echocardiography in chronic asymptomatic alcoholic patients. *Cardiovasc Toxicol* 2015 Apr;15(2):189-196. doi: 10.1007/s12012-014-9284-9.
22. Stojicić 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;35:1599-1606.
23. Kupari M, Koskinen P, Suokas A. Left ventricular size, mass and function in relation to the duration and quantity of heavy drinking in alcoholics. *AmJ Cardiol* 1991;67:274-279.
24. George A, Figueredo VM. Alcoholic cardiomyopathy: a review. *J Card Fail* 2011; 17:844-849.
25. Mathews E. C. Jr., Gardin J. M, Henry W. L et al. Echocardiographic abnormalities in chronic alcoholics with and without overt congestive heart failure. *The American Journal of Cardiology*. 1981;47(3):570–578. doi: 10.1016/0002-9149(81)90540-3.
26. Urbano-Marquez A, Estruch R, Navarro-Lopez F, Grau J. M, Mont L, Rubin E. The effects of alcoholism on skeletal and cardiac muscle. *The New England Journal of Medicine*. 1989;320(7):409–415. doi: 10.1056/nejm198902163200701.
27. Kino M, Imamitchi H, Morigutchi M, Kawamura K, Takatsu T. Cardiovascular status in asymptomatic alcoholics, with reference to the level of ethanol consumption. *Br Heart J* 1981;46:545-551.
28. 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;67:274-279.
29. Fernández-Solà, J., Nicolás, J. M., Paré, J. C., Sacanella, E., Fatjó, F., Cofán, M., et al. (2000). Diastolic function impairment in alcoholics. *Alcoholism, Clinical and Experimental Research*, 24, 1830–1835.
30. Lazarević AM, Nakatani S, Nesković AN, Marinković J, Yasumura Y, Stojicić 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;35:1599-1606.
31. 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; 320:409-415.
32. Kalayci A, Karabay C.Y, Kocabay G, Oduncu V. Subclinical Left Ventricular Dysfunction in Chronic Asymptomatic Alcoholic Patients. *Kosuyolu Heart Journal* 19(3):154-160. DOI: 10.5578/khj.21056
33. Hung C, Gonçalves A, Lai Y, Lai Y et al. Light to Moderate Habitual Alcohol Consumption Is Associated with Subclinical Ventricular and Left Atrial Mechanical Dysfunction in an Asymptomatic Population: Dose-Response and Propensity Analysis. *J Am Soc Echocardiogr* 2016 Nov;29(11):1043-1051.e4. doi: 10.1016/j.echo.2016.07.014.