

## Low to Moderate Alcohol Consumption and Myocardial Ischemia on Exercise Stress Echocardiography

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### Abstract

**Background:** The impact of alcohol consumption on the development of myocardial ischemia remains uncertain. Studies diverge whether low to moderate alcohol consumption provides cardioprotection or whether it is a risk factor for myocardial ischemia.

**Objective:** To study the relationship between low to moderate alcohol consumption and myocardial ischemia on exercise stress echocardiography (ESE).

**Methods:** Cross-sectional study with 6,632 patients with known or suspected coronary artery disease undergoing ESE between January/2000 and December/2015. The patients were divided into two groups: G1, composed of 2,130 (32.1%) patients whose report showed maximal consumption of 1 drink per day on average for women or of 2 drinks per day for men; G2, composed of individuals denying any alcohol consumption. For comparing between the groups, Student t test was used for quantitative variables, and chi-square test or Fisher exact test, for categorical variables. The significance level adopted was  $p < 0.05$ . Logistic regression was also used to evaluate independent risk factors for myocardial ischemia.

**Results:** G1 had a higher number of men (77.1%;  $p < 0.001$ ), lower mean age ( $54.8 \pm 10.3$  years old;  $p < 0.001$ ) and higher frequency of myocardial ischemia on ESE ( $p = 0.014$ ). Age, male sex, dyslipidemia, systemic arterial hypertension, diabetes mellitus, smoking and family history were independently associated with myocardial ischemia on ESE. Independent association between low to moderate alcohol consumption and myocardial ischemia on ESE (OR 0.96; 95%CI: 0.83 to 1.11) was not observed. However, age, male sex, smoking and dyslipidemia were associated with alcohol consumption.

**Conclusion:** Low to moderate alcohol consumption was not an independent predictor of myocardial ischemia on ESE. Nevertheless, we observed a predominance of the male sex, dyslipidemia and smoking habit, important predictors of myocardial ischemia, in the group of alcohol consumers. (International Journal of Cardiovascular Sciences. 2018;31(3)235-243)

**Keywords:** Alcoholic Beverages; Alcohol Drinking; Risk Factors; Coronary Artery Disease; Echocardiography, Stress.

### Introduction

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality worldwide.<sup>1,2</sup> In Brazil, that scenario is not different, because cardiovascular diseases account for more than one third of the deaths

annually.<sup>3</sup> Thus, one of the most frequent challenges in daily cardiology practice is the early assessment of CAD. Such investigation implies a substantial and growing burden to health systems, especially considering the characteristics of the Brazilian population, of which approximately two thirds use the Brazilian Unified

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Health System. Therefore, it is mandatory to identify high-risk groups that would benefit from further investigation, and low-risk groups that would not require additional investigative procedures.<sup>4,5</sup>

There are numerous effects of alcohol consumption, most of which are harmful to health.<sup>6,7</sup> While its influence on deaths from external causes and on morbidity and mortality due to neoplasms is often reported,<sup>8</sup> the impact of low to moderate alcohol consumption on the prognosis of CAD remains uncertain.<sup>6,8</sup> Recent studies have described moderate alcohol consumption as cardioprotective,<sup>7-11</sup> although that association has been questioned.<sup>12-15</sup>

The definition of moderate alcohol consumption varies widely (from 5 to 60 grams of ethanol per day); however no more than one drink daily of alcoholic beverage for women and up to two drinks daily for men are commonly considered moderate alcohol consumption.<sup>10-11</sup> More specifically, one drink of alcoholic beverage can be defined as approximately 330 mL of common beer, 100 mL of wine, or 30 mL of distilled beverage.<sup>16</sup>

Stress echocardiography is a well-established non-invasive test to assess myocardial ischemia in patients with suspected or known CAD, to determine its diagnosis and prognosis, and to aid in therapeutic decision-making.<sup>17</sup> Exercise stress echocardiography (ESE) is the first choice for patients with preserved physical capacity, being safer and more versatile than pharmacological stress echocardiography.<sup>18</sup>

This study was aimed at assessing the relationship between low to moderate alcohol consumption and the presence of myocardial ischemia on ESE.

## Methods

This analytical and descriptive cross-sectional study was carried out from January 2000 to December 2015.

### Patients

The convenience sample consisted initially of 10827 patients with suspected and/or established CAD, who underwent ESE at the accredited Echocardiography Laboratory (ECOLAB) of the São Lucas Hospital and Foundation (*Instituto Qualisa de Gestão - IQG*), in Aracaju city, Sergipe State. All patients older than 25 years referred to the service were included in this study, except for those who refused to participate. Of those, 27 patients were excluded due to their average intake of more

than one drink of alcoholic beverage daily for women and more than two drinks for men. In addition, 4,168 individuals did not report the frequency of consumption, resulting in a final sample of 6,632 patients. The isolated or combined indications for ESE were: assessment of chest pain; preoperative assessment for non-cardiac surgery; positive exercise test (ET) for myocardial ischemia in patients at low risk for CAD; negative ET for myocardial ischemia in patients at intermediate risk for CAD; arrhythmia during ET; stratification of previously established CAD; and risk stratification after acute coronary syndrome.

The study patients were divided into two groups according to their frequency of alcoholic beverage intake as follows: G1 - 2,130 (32.1%) patients reporting a maximum daily consumption of one drink (women) or two drinks (men); and G2 - 4,502 (67.9%) individuals reporting no alcohol intake.

### Clinical characteristics

The clinical data were collected and recorded during an interview conducted before the ESE, by use of a standard questionnaire assessing: weight; height; symptoms, such as dyspnea and chest pain; medications; risk factors for CAD; family or personal history of heart disease; and data regarding previous CAD, such as acute myocardial infarction, and percutaneous and surgical myocardial revascularization. In addition, the results of previous laboratory and cardiovascular tests were recorded.

Alcohol consumption was quantified by use of self-report as follows: low to moderate alcohol consumption, consisting of a maximum daily intake of two drinks of alcoholic beverage for men, and of one drink for women. One drink of alcoholic beverage can be defined as approximately 330 mL of common beer, 100 mL of wine, or 30 mL of distilled beverage.<sup>10,16</sup> Based on those parameters and on the reports in the interview, the average daily consumption for each patient was estimated.

Obesity was defined as a body mass index greater than 30 kg/m<sup>2</sup>. Hypercholesterolemia was defined as total cholesterol serum levels greater than 200 mg/dL (after 12-hour fasting), while hypertriglyceridemia, as triglyceride serum levels greater than 150 mg/dL (after 12-hour fasting) or use of lipid-lowering agents (statins and/or fibrates).

Systemic arterial hypertension was identified in the presence of systolic blood pressure  $\geq$  140 mm Hg and/

or diastolic blood pressure  $\geq 90$  mm Hg, measures taken on the upper limb, at rest and under ideal conditions, and repeated and confirmed, or when antihypertensive agents were used.

Diabetes mellitus was identified in the presence of: fasting glycemia  $\geq 126$  mg/dL; or glycemia  $\geq 200$  mg/dL after 2 hours of oral glucose overload (75g); or random glycemia  $\geq 200$  mg/dL associated with classic symptoms of hyperglycemia; or use of oral hypoglycemic agents.

### Exercise stress echocardiography

The protocol consisted initially in performing a 12-lead electrocardiogram (ECG) and a resting echocardiography after clinical investigation. Then, ET was performed on a treadmill, and, right after, new echocardiographic images were acquired.

All patients were submitted to the standard Bruce or Ellestad protocol during ET. Heart rate was monitored continuously, and the patients were encouraged to achieve their peak physical effort. For metabolic calculations, maximum oxygen consumption at peak exercise ( $VO_2\text{max}$ ) was obtained indirectly by use of the formula:  $VO_2\text{max} = 14.76 - 1.379t + 0.451t^2 - 0.012t^3$ , where  $t$  is the duration of ET in minutes.<sup>19</sup> Load was expressed in metabolic equivalents, where 1 MET corresponds to 3.5 mL/kg·min of inhaled  $VO_2$  at rest.<sup>20</sup> During ET, the individuals were continuously monitored by use of 3-lead ECG.

The electrocardiographic ischemic changes during exercise were horizontal or descending ST-segment depressions  $\geq 1$  mm for men, and  $\geq 1.5$  mm for women, at 0.08 second from J point.<sup>21</sup>

The ET was performed in an ergonomically designed environment with a continuously trained team, at a reference hospital in cardiology, accredited for specific assessment. The suspension of beta-blockers three days before the ET is recommended routinely, while the other usual drugs are maintained.

The ET was performed with a Hewlett Packard/Phillips SONOS 5500 device until 2012, and, from that year on, with a Phillips IE-33 device, abiding by the technical aspects classically described by Schiller et al.<sup>22</sup> The two-dimensional echocardiographic images were obtained in parasternal and apical acoustic windows, at rest and immediately after exertion, with the patient lying in the left lateral decubitus position and simultaneous electrocardiographic recording.

Left ventricular segmental wall motion was assessed by an experienced level III echocardiographer, as recommended by the American Society of Echocardiography.<sup>23</sup> Left ventricular segmental wall thickening was quantitatively assessed at rest and after exertion by use of the model of 16 segments graded as: 1, normal; 2, hypokinetic; 3, akinetic; 4, dyskinetic. The left ventricular wall motion score index (LVWMSI) was calculated at rest and during exertion as the addition of the scores of each of the 16 segments divided by the number of segments assessed at a given time. A LVWMSI of 1 corresponds to normality, between 1.1 and 1.6 represents mild dysfunction, and between 1.61 and 2, moderate dysfunction. Values greater than 2 represent significant dysfunction.<sup>22</sup> The difference between the LVWMSI at exertion and at rest is the  $\Delta$ LVWMSI. The development of a new wall motion change or worsening of the existing dyssynergy ( $\Delta$ LVWMSI  $\neq 0$ ) was considered indicative of myocardial ischemia.

### Statistical analysis

The quantitative variables were described as mean and standard deviation. According to the assumption of sample normality, assessed by use of the Kolmogorov-Smirnov test, the quantitative variables were assessed by use of Student  $t$  test for independent groups. For the categorical variables, absolute frequency and percentage were used. To compare the characteristics of categorical variables between the two groups, chi-square test or Fisher exact test, when more appropriate, was used.

To assess the association between the variable outcome (myocardial ischemia on ESE) and the associated factors, logistic regression was performed with backward-Wald method. To enter the initial model, all variables with  $p < 0.25$  were admitted, while to remain in the model,  $p < 0.05$  was adopted. The variables were entered into and removed from the model manually, depending on meeting the assumption. The Statistical Package for the Social Sciences (SPSS), version 22.0 (Chicago, IL), was used in the statistical analysis.

### Ethical aspects

This study abided by the ethical principles that regulate human experimentation, and all patients provided written informed consent. This study was approved by the Committee in Ethics and Research of the Sergipe Federal University (CAAE 1818.0.000.107-06).

## Results

This study assessed 6,632 patients, 3,257 (49.1%) of the male sex, mean age of  $57.6 \pm 11.1$  years (25 - 98 years). Low to moderate alcohol consumption (G1) was reported by 2,130 individuals (32.1%), while 4,502 (67.9%) individuals (G2) reported no alcohol intake.

In G1, 21.8% of the patients showed positive results for myocardial ischemia on ESE, with a statistically significant relationship between low to moderate alcohol consumption and myocardial ischemia, as compared to G2.

### Clinical characteristics of the groups

In G1, there were a higher relative frequency ( $p < 0.001$ ) of male individuals, lower mean age and higher percentage of smokers. Regarding the other sociodemographic characteristics, G1 showed a significantly ( $p < 0.001$ ) higher educational level, higher abdominal circumference values and lower frequency of sedentary lifestyle as compared to G2 (Table 1).

The major clinical variables that associated with myocardial ischemia on ESE are shown in Table 2. Of the major clinical findings, only history of sedentary lifestyle and diagnosis of obesity were not significant on univariate analysis for the presence of myocardial ischemia.

### Echocardiographic and exercise test characteristics of the groups

The G2 showed a higher number of patients without evidence of myocardial ischemia on ESE. Fixed myocardial ischemia was the most frequent type found in G1. Greater sizes of the aorta and left atrium were observed in G1, while G2 showed a higher frequency of diastolic dysfunction. Of the ET variables, ST-segment depression and chronotropic insufficiency were more frequent in G1 and in G2, respectively (Table 3).

### Logistic regression analysis

The multivariate analysis by use of logistic regression of the clinical data available showed that age, male sex, diabetes mellitus, systemic arterial hypertension, dyslipidemia, smoking habit and family history were independently associated with myocardial ischemia (Table 4). When assessing those confounding factors of the model, there was no association between low to moderate alcohol consumption and myocardial ischemia on ESE.

**Table 1 - Clinical characteristics of patients consuming a low to moderate amount of alcohol (G1) or none (G2), submitted to exercise stress echocardiography**

Variables	G1 (n = 2,130)	G2 (n = 4,502)	P*
Male sex	1,643 (77.1%)	1,614 (35.9%)	< 0.001
Age	$54.8 \pm 10.3$	$59.0 \pm 11.3$	< 0.001
Previous symptoms			
Asymptomatic	1,088 (52.3%)	1,808 (41.2%)	
Typical chest pain	135 (6.5%)	290 (6.6%)	< 0.001
Atypical chest pain	762 (36.6%)	2,034 (46.4%)	
Dyspnea	103 (4.9%)	269 (6.1%)	
Obesity	509 (24%)	991 (22.1%)	0.088
Weight	$78.3 \pm 14.2$	$70.7 \pm 14.0$	< 0.001
Height	$1.68 \pm 0.09$	$1.61 \pm 0.09$	< 0.001
Abdominal circumference	$96.6 \pm 11.9$	$93.3 \pm 12.4$	0.001
Systemic arterial hypertension	1,269 (59.8%)	2,786 (62%)	0.078
Diabetes mellitus	274 (12.9%)	542 (12.1%)	0.339
Dyslipidemia	1,185 (55.8%)	2,457 (54.7%)	0.414
Smoking habit	157 (7.4%)	140 (3.1%)	< 0.001
Family history	1,252 (58.9%)	2,671 (59.5%)	0.690
Physical activity			
None	997 (49.9%)	2,408 (56.9%)	
Active	985 (49.3%)	1,789 (42.3%)	< 0.001
Athlete	18 (0.9%)	34 (0.8%)	
Old infarction	113 (5.5%)	191 (4.4%)	0.049
Recent infarction	8 (0.4%)	10 (0.2%)	0.258
Revascularization	122 (5.9%)	215 (4.9%)	0.092
Angioplasty	174 (8.5%)	312 (7.2%)	0.064
Stent	122 (5.9%)	214 (4.9%)	0.084

(\*) The qualitative variables were calculated by use of Pearson chi-square test, and the quantitative variables, by use of Student t test for independent samples, according to the normality assumption of the sample.

In addition, age, male sex, smoking habit and dyslipidemia associated with low to moderate alcohol consumption (Table 5).

**Table 2 - Univariate analysis of the clinical parameters associated with the presence of myocardial ischemia on exercise stress echocardiography**

Variables	Odds Ratio	95% CI	p*
Alcohol consumption	1.15	1.01-1.30	0.035
Male sex	1.69	1.50 - 2.90	< 0.001
Age	1.03	1.02-1.03	< 0.001
Obesity	1.02	0.88-1.18	0.76
Diabetes mellitus	1.99	1.70-2.35	< 0.001
Systemic arterial hypertension	2.16	1.88-2.47	< 0.001
Dyslipidemia	2.25	1.98-2.56	< 0.001
Smoking habit	1.79	1.39-2.31	< 0.001
Family history	1.82	1.59-2.07	< 0.001
Sedentary lifestyle	1.07	0.94-1.21	0.285

CI: confidence interval. (\*) The qualitative variables were calculated by use of Pearson chi-square test, and the quantitative variables, by use of Student t test for independent samples, according to the normality assumption of the sample.

**Table 3 - Echocardiographic and exercise test characteristics of patients consuming a low to moderate amount of alcohol (G1) or none (G2), submitted to exercise stress echocardiography**

Variables	G1 (n = 2,130)	G2 (n = 4,502)	p*
Ischemia			
None	1,666 (78.2%)	3,621 (80.4%)	
Induced	195 (9.2%)	430 (9.6%)	0.014
Fixed	211 (9.9%)	359 (8%)	
Fixed and induced	58 (2.7%)	91 (2%)	
Aorta	3.3 ± 0.4	3.1 ± 0.4	< 0.001
Left atrium	3.9 ± 0.4	3.8 ± 0.4	< 0.001
E wave velocity	68.4 ± 15.1	70.9 ± 17.1	0.778
E' wave velocity	8.0 ± 4.1	7.6 ± 2.3	0.140
E/E' ratio	9.3 ± 2.8	10.0 ± 3.6	0.347
Ejection fraction	67% ± 6.4	67% ± 6.5	0.133

LVWMSI at rest	1.02 ± 0.09	1.01 ± 0.08	0.246
LVWMSI on exertion	1.03 ± 0.09	1.02 ± 0.09	0.459
Diastolic function			
Normal	294 (17.4%)	473 (13.6%)	
Relaxation deficit	851 (50.3%)	1,918 (55.1%)	0.001
Pseudonormal	540 (31.9%)	1,075 (30.9%)	
Restrictive	8 (0.5%)	17 (0.5%)	
ST-segment depression	1,355 (64.1%)	2,793 (62.5%)	< 0.001
Left bundle-branch block	66 (3.1%)	183 (4.1%)	0.054
Simple arrhythmias	539 (25.3%)	1,309 (29.1%)	0.001
Severe arrhythmias **	4 (0.2%)	16 (0.4%)	0.245
NSVT	-	2 (< 0.1%)	0.330
Atrial fibrillation	1 (0.1%)	2 (0.1%)	0.999
Ventricular extrasystole	63 (3.8%)	105 (3.2%)	0.242
Supraventricular extrasystole	19 (1.1%)	43 (1.3%)	0.654
Supraventricular tachycardia	4 (0.2%)	8 (0.2%)	0.999
Chronotropic insufficiency	160 (7.5%)	440 (9.8%)	0.003

LVWMSI: left ventricular wall motion score index; NSVT: non-sustained ventricular tachycardia; (\*\*) Ventricular tachycardia or ventricular fibrillation. (\*) The qualitative variables were calculated by use of Pearson chi-square test, and the quantitative variables, by use of Student t test for independent samples, according to the normality assumption of the sample.

## Discussion

Low to moderate alcohol consumption related with myocardial ischemia on ESE, but was not an independent predictor of positivity on that test. The literature is controversial about the association between alcohol consumption and ischemic heart diseases. The effect of alcohol on patients with myocardial ischemia has been reported as protective in a daily alcohol intake of up to one drink<sup>6,7</sup> or two drinks.<sup>9,10</sup> Other studies have reported alcohol consumption as a risk factor for myocardial ischemia at an average consumption of at least one drink daily<sup>13</sup> or at any daily amount.<sup>12,14</sup> Divergences and lack of correlation between myocardial

**Table 4 - Multivariate logistic regression with clinical parameters associated with the presence of myocardial ischemia on exercise stress echocardiography**

Variables	Odds Ratio	95% CI	p
Alcohol consumption	0.94	0.81-1.01	0.463
Male sex	1.83	1.62-2.09	< 0.001
Age	1.02	1.02-1.03	< 0.001
Diabetes mellitus	1.52	1.28-1.80	< 0.001
Systemic arterial hypertension	1.55	1.34-1.79	< 0.001
Dyslipidemia	1.84	1.61-2.1	< 0.001
Smoking habit	2.03	1.55-2.64	< 0.001
Family history	1.69	1.47-1.93	< 0.001

CI: confidence interval.

**Table 5 - Multivariate logistic regression with clinical parameters associated with low to moderate alcohol consumption**

Variables	Odds Ratio	95% CI	p
Myocardial ischemia à ESE	0.96	0.83-1.11	0.603
Male sex	5.88	5.21-6.63	< 0.001
Age	0.97	0.96-0.97	< 0.001
Smoking habit	2.73	2.11-3.54	< 0.001
Dyslipidemia	1.51	1.02-1.29	0.017

ESE: exercise stress echocardiography; CI: confidence interval.

ischemia and alcohol intake evidenced in certain studies can be explained by individual differences inherent in genetic characteristics.<sup>11</sup>

Roerecke and Rehm<sup>6</sup> in a systematic review, have assessed 44 observational studies relating ischemic heart diseases to low to moderate alcohol consumption, between 1980 and 2010, in a total of 957,684 participants. Those authors have shown that, although there is some confirmed cardioprotective association, substantial heterogeneities remain unexplained and the confidence

intervals were relatively wide, particularly between one and two drinks of alcoholic beverage daily. Therefore, the cardioprotection related to alcohol intake has been described as an association that cannot be assumed, even when assessing the level of alcohol consumption.

The variables male sex, dyslipidemia and smoking habit - independent predictors of low to moderate alcohol consumption in the present study - also showed a close relationship with myocardial ischemia. In accordance with the literature, greater frequency of alcohol intake is observed among men<sup>7,13</sup> and together with the smoking habit,<sup>13,14</sup> widely identified as risk factors for myocardial ischemia.<sup>17</sup> Perissinotto et al.<sup>24</sup> have evidenced higher serum levels of LDL cholesterol and total cholesterol among the elderly whose alcohol intake was moderate, as in the present study, although that consumption has been reported as inversely associated with dyslipidemia.<sup>11,14</sup>

The literature lacks ET and echocardiography data related to low to moderate alcohol consumption, and significant differences were evidenced in the present study. Statistical significance was observed in the relationship between alcohol consumption and larger size of the aorta and left atrium, as well as with the higher frequency of ST-segment depression and lower frequency of diastolic dysfunction and chronotropic insufficiency.

Regarding the limitations of this study, those inherent in any observation study stand out, in which the variables not measured can contribute to the statistical differences between the groups. In addition, distinct intervals of alcohol intake could not be accurately quantified, and neither could the duration of alcohol consumption, the type of alcoholic beverage used and the previous history of that habit.

## Conclusion

Low to moderate alcohol consumption showed not to be an independent predictor of the presence of myocardial ischemia on ESE. In the group of alcohol consumers, there were more individuals of the male sex, dyslipidemic and smokers, which are important predictors of myocardial ischemia.

## Author contributions

Conception and design of the research: Fontes VJB, Oliveira JLM. Acquisition of data: Fontes VJB, Souto MJS, Conceição FMS, Telino CJCL, Silveira MS,

Dória JAS, Matos CJO, Oliveira JLM. Analysis and interpretation of the data: Fontes VJB, Souto MJS, Sousa ACS, Melo EV, Conceição FMS, Telino CJCL, Silveira MS, Dória JAS, Matos CJO, Oliveira JLM. Statistical analysis: Melo EV. Writing of the manuscript: Fontes VJB, Souto MJS, Sousa ACS, Melo EV, Conceição FMS, Telino CJCL, Matos CJO, Oliveira JLM. Critical revision of the manuscript for intellectual content: Fontes VJB, Souto MJS, Sousa ACS, Melo EV, Conceição FMS, Telino CJCL, Matos CJO, Oliveira JLM. Supervision / as the major investigador: Oliveira JLM.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

This study is not associated with any thesis or dissertation work.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Sergipe under the protocol number CAAE 1818.0.000.107-06. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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