# An Evaluation of the Effectiveness of Water, Milk and Natural Lemon Juice in Hepatic Biliary Secretion of <sup>99m</sup>tc-Mibi Radiopharmaceutical in Myocardial Perfusion Imaging

S.H. Mousavie Anijdan (PhD)<sup>1</sup>, A. Gholami (MD)<sup>•2</sup>

1.Social Determinants of Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, I.R.Iran 2.Cancer Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, I.R.Iran

J Babol Univ Med Sci; 20(1); Jan 2018; PP: 7-12 Received: Jun 11<sup>th</sup> 2017, Revised: Sep 6<sup>th</sup>2017, Accepted: Nov 21<sup>st</sup>2017.

#### ABSTRACT

**BACKGROUND AND OBJECTIVE:** Interfering sub-diaphragmatic activity in the liver, bile ducts and intestines is one of the complications of myocardial perfusion imaging in the diagnosis of coronary artery disease. The aim of this study was to compare the effectiveness of water, milk and natural lemon juice on liver secretion and reduction of <sup>99m</sup>Tc-sestamibi radiopharmaceutical radiation in this type of imaging.

**METHODS:** This clinical study was performed on 100 female patients referred to the Shahid Beheshti Hospital in Babol for myocardial perfusion imaging using SPECT method. These patients were randomly divided into 4 groups: patients receiving no drink (group 1), patients receiving 250 ml water (group 2), patients receiving 250 ml high-fat milk (group 3), and patients receiving 250 ml diluted lemon juice was (group 4). After measuring heart and liver absorption, their ratio was calculated (heart/liver). The rate of reduction of interfering sub-diaphragmatic activity after the use of these drinks in different groups was evaluated based on visual and semi-quantitative assessments.

**FINDING:** The four studied groups did not differ significantly in terms of age, weight, and body mass index. The H/L ratio in group 1 was  $0.13\pm0.038$ , in the group 2 was  $0.15\pm0.039$ , in the group 3 was  $0.17\pm0.055$  and in the group 4 was  $0.15\pm0.039$ . Statistical analysis showed that interfering sub-diaphragmatic activity was only significant in group 3 in comparison with group 1 (p=0.027). In addition, based on visual and semi-quantitative assessments of raw data, only in group 3, 18 out of 25 patients had less interfering sub-diaphragmatic activity, which was significant compared to group 1 (p=0.001).

**CONCLUSION:** The results of the study showed that drinking at least 250 ml high-fat milk can reduce the interfering sub-diaphragmatic activity.

KEY WORDS: Myocardial perfusion imaging, Coronary arteries, Radiopharmaceutical Technetium.

#### Please cite this article as follows:

Mousavie Anijdan SH, Gholami A. An evaluation of the Effectiveness of Water, Milk and Natural Lemon Juice in Hepatic Biliary Secretion of <sup>99m</sup>tc-Mibi Radiopharmaceutical in Myocardial Perfusion Imaging. J Babol Univ Med Sci. 2018;20(1):7-12.

Corresponding author: A. Gholami (MD)
Address: Department of Radiology and Radiotherapy, Faculty of Medicine, Babol University of Medical Sciences, Babol, I.R.Iran.
Tel: +98 11 32252071
E-mail: amir\_gholami\_4@yahoo.com

# Introduction

**C**oronary Artery Disease (CAD) is a common cardiovascular disease that kills many people in modern societies, particularly at higher ages. Typically, electrocardiography (ECG) exercise testing, single-photon emission computed tomography (SPECT), and cardiac angiography are used to diagnose CAD. Myocardial perfusion imaging (MPI) is used in nuclear medicine as a non-invasive method for the diagnosis and prognosis of coronary artery disease (1, 2).

MPI is often performed in two modes of stress and rest separately, and it is possible to detect myocardial perfusion defects as well as heart failure or infarction by comparing the two scans. The stress phase occurs in two ways; pharmacological stress or exercise. Radioactive substances (radiopharmaceuticals) are used in both phases of the imaging. Currently, the most commonly radiopharmaceuticals used in this type of imaging are technetium (99mTc) derivatives such as 99mTc-sestamibi and 99mTc-tetrofosmin. Because of having optimum photon energy, technetium increases the contrast and provides high-quality diagnostic images (3, 4). These radiopharmaceuticals are cleansed by the liver and excreted through the extrahepatic biliary system, resulting in interfering subdiaphragmatic radioactivity in the liver, bile ducts and intestines (5, 6).

Therefore, the appearance of this radioactivity in the sub-diaphragmatic area may produce false negative and false positive results in the studies of myocardial perfusion imaging (8, 7). Due to the proximity of the liver and the intestine to the inferior wall of myocardium, reliable judgment about CAD in this area can be difficult (9). The appearance of significant subdiaphragmatic radioactivity is unpredictable in myocardial perfusion imaging. Therefore, sufficient hepatobiliary clearance and digestive tract clearance is necessary to obtain high quality images for interpretation (2). Reliable interpretation of heart scan can be problematic due to the disturbing radioactivity in the sub-diaphragm, especially in the liver, bile ducts and intestines. Some of the available solutions include the use of some foods and fluids to reduce or eliminate the problem by increasing the hepatobiliary and intestinal transmission of radiopharmaceuticals, which include eating high-fat foods, drinking milk, drinking milk and water, injection of cholecystokinin, and administration of metoclopramide. High-fat foods release cholecystokinin (CCK), which results in

increased biliary secretion and evacuation of the gallbladder, thereby leading to increased hepatobiliary clearance and reduced interfering sub-diaphragmatic radioactivity (10-12). In the study of Hofman et al., the group that received milk had a significant reduction in sub-diaphragmatic radioactivity compared to the group that received water, but interpretation of the images was not improved (13). Furthermore, Purbhoo et al. showed that diluted lemonade and milk significantly reduced the interfering sub-diaphragmatic and hepatic radioactivity in heart perfusion imaging using 99mTcsestamibi radiopharmaceuticals, which was more pronounced in the group receiving milk (14). In the study of Malek et al., the group that received milk had significantly lower interfering radioactivity than those receiving lemon juice and water, resulting in higher image quality (15).

Two methods are used in the stress phase: exercise (treadmill) or medication. To cause pharmaceutical stress, vasodilators such as dipyridamole or adenosine are commonly used to create coronary arterial hyperemia. Interfering splanchnic radioactivity is more prominent in pharmaceutical stress method compared to exercise method due to the effect of splanchnic vasodilation. According to available information, acidic drinks increase liver secretion and bile duct movements (13). Therefore, water, milk and diluted lemon juice were used in this study as beverages to investigate their effect on the hepatobiliary secretion of <sup>99m</sup>Tc-sestamibi radiopharmaceutical, which results in reduction in interfering sub-diaphragmatic radioactivity.

#### **Methods**

After being approved by the ethics committee of Babol University of Medical Sciences with the code of ethics MUBABOL.REC.1394.26 and the code IRCT: 2015080123441N1, this clinical trial was conducted among 100 female patients referred to the nuclear medicine department of Shahid Beheshti Hospital in Babol for myocardial perfusion imaging using SPECT method. Patients with previous history of cholecystectomy, hepatobiliary disease, peptic ulcer, diabetes, history of myocardial infarction, heart valve disease and heart failure were included. The stress phase of heart scan is typically performed first in Shahid Beheshti Hospital in Babol. Considering the normal myocardial perfusion in stress phase, it is possible to ignore the next phase of the study (resting

phase), which reduces the patient's radiation. Thus, in order for such a strategy to work, getting high-quality image in the stress phase is very important. Accordingly, this study was carried out only in the stressful step using the pharmaceutical method (prescribing dipyridamole).

Considering that most patients referred for heart scan were female, and to have patients with similar characteristics in terms of gender, age and body mass index, only female patients were selected in this study for ease of work. Patients referred for myocardial perfusion imaging using SPECT method were randomly divided to four groups in the stress phase (with drug): patients receiving no drink (group 1), patients receiving 250 ml water (group 2), patients receiving 250 ml high-fat milk (group 3), and patients receiving 250 ml diluted lemon juice (100 ml of lemon juice in 150 ml of water) (group 4). 10 minutes after receiving the radiopharmaceutical, patients received a drink depending on the group. Thirty minutes after receiving the target drink, a 2-dimensional (planar) image of the patients was captured in the anterior view for 90 seconds. Then, the absorption ratio of the heart to liver (H/L ratio) was estimated for all patients by drawing ROIs (regions of interest) on the heart and right lobe of the liver. In addition, after capturing the images, a visual and semi-quantitative assessment of sub-diaphragmatic radioactivity was done. Then, SPECT imaging was done with a SIEMENS Orbiter Nuclear Gamma Camera equipped with a low-energy, high-resolution autocollimator by routine (images were recorded over 180° around the patient in 64×64 matrices with an acquisition time of 25 seconds per projection [32 projections] with 1.2 zoom factor). Subsequently, pharmaceutical radiation in the liver, bile ducts and intestines were judged in all patients after processing the SPECT images. The visual and semi-quantitative raw data analysis was performed according to the study of Hofman et al. (13).

The presence of interfering sub-diaphragmatic radioactivity was categorized as follows: Zero: the absence of interfering sub-diaphragmatic radioactivity, One: sub-diaphragmatic radioactivity lower than diaphragmatic radioactivity, Two: sub-diaphragmatic radioactivity, and Three: sub-diaphragmatic radioactivity higher than diaphragmatic radioactivity. Patient characteristics and H/L ratio are expressed as mean±standard deviation. The difference in mean H/L ratio among the groups was assessed by one-way ANOVA. The comparison

between the groups was also performed by Tukey posthoc test. Chi-square test was used to determine the effect of different drinks on interfering subdiaphragmatic radioactivity and p<0.05 was considered statistically significant.

## **Results**

The mean age in group 1 (without receiving) was  $54.72\pm9.68$ , in group 2 (water) was  $55.44\pm9.98$ , in group 3 (high-fat milk) was  $52.24\pm10.78$ , and in group 4 (lemon juice) was  $49.56\pm10.33$  years old. The results of statistical tests showed that the variables of age (p=0.97), weight (p=0. 93) and BMI (p=0.95) did not show any significant difference between groups. The H/L ratio in group 2 was  $0.15\pm0.039$  and in group 4 was  $0.15\pm0.039$ .

In comparing the mean H/L ratio in different groups, a statistically significant difference was observed (p=0.02). Consequently, the Tukey post-hoc test showed that this difference was significant between the group receiving 250 ml of high-fat milk (group 3) compared to the group without drinking (group 1) (p=0.01) (Fig 1). As shown in Figure 1, the mean H/L ratio in patients with any intervention was significantly higher than that of the group without receiving it, but this increase was statistically significant only in the group receiving high-fat milk (group 3) (p=0.01). The findings of the visual assessment of the severity of interfering subdiaphragmatic radioactivity are shown in Table 2.

In group 1, zero (0%) patients had no interfering sub-diaphragmatic radioactivity, 3 (12%) patients had diaphragmatic radioactivity higher than interfering sub-diaphragmatic radioactivity, 14 (56%) patients had diaphragmatic radioactivity equal to interfering subdiaphragmatic radioactivity, and 8 (32%) patients had diaphragmatic radioactivity lower than interfering subdiaphragmatic radioactivity. These values in group 2 were 0 (0%), 4 (16%), 13 (52%) and 8 (32%), in group 3 were 4 (16%), 14 (56%), 5 (20%) and 2 (8%) and in group 4 were 2 (8%), 4 (16%), 10 (40%) and 9 (36%), respectively. The result of the chi-square test showed that there was a significant relationship between the study groups and the severity of interfering subdiaphragmatic radioactivity (p=0.001) (Table 2). In the quantitative visual assessment, most patients in groups 1, 2 and 4 had almost equal diaphragmatic absorption and sub-diaphragmatic absorption, and only in patients in group 3, most patients had diaphragmatic absorption higher than sub-diaphragmatic absorption. Moreover, while one third of patients in groups 1, 2, and 4 had

higher sub-diaphragmatic absorption, these values were significantly reduced in patients in group 3.

Tat	ole 1. Demogra	aphic charact	eristics of the s	study patients	
Variable	Group 1	Group 2	Group 3	Group 4	<b>P-value</b>
Age (year)	54.72±9.68	55.44±9.98	52.24±10.78	49.56±10.33	0.97
Weight (kg)	74.32±12.3	74.2±12.8	73.76±11.54	75.48±15.19	0.93
BMI(kg.m2)	30±4.68	29.05±4.61	29.74±6.41	29.49±5.5	0.95



Figure 1. H/L ratio of different groups of patients

	$\sim$	•	•	• •					•								• .	•		<b>no</b> 4		
Toble 7		'omnoricon o	÷ •	1710110	occoccmont	<b>nt</b>	intor	0	nna	CIID	dia	nhra	amoti	O P	odio	ontis		7 11	s dat	toront	aro	inne
1 2010 2.	· •	.011110/11/15/011/0		VISUA	assessment	UI			IIIY	SHU	- 11 21		211AL	L. I.	auro					еен	210	
	~		_			~ ~		_		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~				-								
																					-	

Radiation Severity Group	Lack of interfering radioactivity	Diaphragmatic absorption > sub- diaphragmatic radioactivity	Diaphragmatic absorption=sub- diaphragmatic radioactivity	Diaphragmatic absorption < sub- diaphragmatic radioactivity
Not receiving(1)	0(0)	3(12)	14(56)	8(32)
Water(2)	0(0)	14(16)	13(52)	8(32)
Milk(3)	4(16)	14(56)	5(20)	2(8)
Lemon juice(4)	2(8)	4(16)	10(40)	9(36)

P=0.001

# Discussion

According to the results of this study, we can use high-fat milk to reduce interfering sub-diaphragmatic radioactivity in myocardial perfusion imaging using SPECT method, which leads to increased image quality. In some studies, milk has been used as a fatty drink for this purpose, and contradictory results have been published in this regard so far (13-17). In some other studies, lemon juice has been mentioned as drink that affects the secretion of bile by stimulating release of secretin from the intestines. Increased release of secretin improves bile secretion, while unlike CCK, it has no significant effect on evacuation of the gallbladder. Therefore, the hepatic clearance increases by <sup>99m</sup>Tc-based radiopharmaceuticals, but interfering

sub-diaphragmatic radioactivity does not increase due to their low effect on evacuation of the gallbladder (14, and 17). In this study, lemon juice did not have a significant effect on the increase in hepatobiliary clearance and the decrease in interfering subdiaphragmatic radioactivity. This finding is in contrast with a number of related studies in this area that emphasize the potential effects of lemon juice on facilitating hepatobiliary clearance accompanied by increased secretion of secretin and decreased interfering sub-diaphragmatic radioactivity (14, 17). Perhaps the reason for this difference is associated with the lack of effect of lemon juice on evacuation of the gallbladder concurrent with the increase in hepatobiliary clearance of bile, because the

physiological discharge of the gallbladder may occur simultaneously with the imaging, which can lead to an increase in interfering sub-diaphragmatic radioactivity. Cherng et al. showed that water, milk and lemon juice are useful for improving the quality of heart scan, because the mean H/L ratio in water, milk and lemon juice groups was higher than that of the group that did not receive any drink. Furthermore, the group that received lemon juice had significantly lower hepatic and sub-diaphragmatic radioactivity than other groups, and consequently, the quality of SPECT images in these patients was higher (17).

However, in our study, only the patients who received milk showed an increase in mean H/L ratio, which reduced the level of interfering subdiaphragmatic radioactivity and increased image quality. In the case of lemon juice, there was no significant increase in the mean H/L ratio compared to the water group and the non-receiving group. In another study, Hofman et al. showed that milk leads to a significant reduction in the level of interfering subdiaphragmatic radioactivity compared to water. The mechanism of this action can be associated with increased stomach volume due to delayed gastric emptying, which is related to high-fat meals, as well as stimulation of gallbladder contraction by the milk and subsequently, the movement of radiopharmaceuticals from liver to duodenum (13).

The findings of this study can be considered similar to our study in terms of the effect of milk on reducing the interfering sub-diaphragmatic radioactivity. However, according to the study of Peace et al., drinking 150 ml of high-fat milk and 450 ml of water together did not increase the radiopharmaceutical's hepatobiliary secretion and did not decrease the interfering sub-diaphragmatic radioactivity (16). Malek et al. also reported similar results in their study. According to their study, among the groups of water and milk (125 ml of water and 125 ml of high-fat milk), lemon juice (250 ml diluted lemon juice), milk (250 ml high-fat milk), water (250 ml) and the group without drinking, only patients who received 250 ml of milk, showed a decrease in interfering sub-diaphragmatic radioactivity and an improvement in the quality of the images, 10 minutes after the injection of <sup>99m</sup>Tc sestamibi (15).

In this study, only patients who received high-fat milk had higher H/L ratio compared with other groups, and this decrease in interfering sub-diaphragmatic radioactivity increased the diagnostic power of the study, which is due to the decrease in artifacts in the images. Therefore, it can be concluded that drinking 250 ml of high-fat milk, 10 minutes after <sup>99m</sup>Tc-MIBI injection, reduces interfering sub-diaphragmatic radioactivity and improves image quality.

## Acknowledgments

Hereby, we express our deepest sense of gratitude and indebtedness to Deputy of Research and Technology of Babol University of Medical Sciences for their financial support. We would also like to thank colleagues at the Nuclear Medicine Department of Shahid Beheshti Hospital, Mr. Ebrahim Kiaganji, Ms. Elham Ahmadi Aghozi and Ms. Fatemeh Ramezani and our Statistics Consultant, Mr. Hemmat Qalinia.

## References

1.Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). J Am CollCardiol. 2003;42(7):1318-1333.

2.Johansen A, Lomsky M, Gerke O, Edenbrandt L, Johansson L, Hansen G, et al. When is reacquisition necessary due to high extra-cardiac uptake in myocardial perfusion scintigraphy? EJNMMI Res. 2013,3(1):20.

3.SridharaBS, BraatS, RigoP, IttiR, CloadP, LahiriA. Comparison of myocardial perfusion imaging with technetium-99m tetrofosmin versus thallium-201 in coronary artery disease. AmJCardiol. 1993;72:1015-19.

4.Haiyan Ma, Sijin Li, Zhifang Wu, Jianzhong Liu, Haiyan Liu, Xiaoshan Guo. Myocardial perfusion imaging with Tctetrofosmin: comparison to 2IOTIimaging and coronary angiography in a phase III multicenter trial. Biomed Res Int. 2013;2013:145427.

5.Higley B, Smith FW, Smith T, Gemmell HG, Das Gupta P, Gvozdanovic DV, et al. Technetium-99m-1,2-bis[bis(2ethoxyethyl) phosphino]ethane: human biodistribution, dosimetry and safety of a new myocardial perfusion imaging agent. J Nucl Med. 1993;34(1):30-8.

6.Wackers FJ, Berman DS, Maddahi J, Watson DD, Beller GA, Strauss HW, et al.Technetium-99m hexakis 2-methoxy isobutyl isonitrile: human biodistribution, dosimetry, safety, and preliminary comparison to thallium-201 for myocardial perfusion imaging. J Nucl Med. 1989;30(3):301-11.

7.1 Middleton GW, Williams JH. Significant gastric reflux of technetium-99m-MIBI in SPECT myocardial imaging. J Nucl Med. 1994;35(4):619-20.

8.Jain D. Technetium-99m labeled myocardial perfusion imaging agents. Semin Nucl Med. 1999;29(3):221-36.

9.Malhotra G, Upadhye TS, Nabar A, Asopa RV, Nayak UN, Rajan MG. Can carbonated lime drink intake prior to myocardial perfusion imaging with Tc-99m MIBI reduce the extracardiac activity that degrades the image quality and leads to fallacies in interpretation?. Clin Nucl Med. 2010;35(3):160-4.

10.Garcia E, Cooke CD, Van Train KF, Folks R, Peifer J, DePuey EG. Technicalaspects of myocardial SPECT imaging with technetium-99m sestamibi. Am J Cardiol. 1990;66(1):80-90.

11.Van Dongen AJ, van Rijk PP. Minimizing liver, bowel, and gastric activity inmyocardial perfusion SPECT. J Nucl Med. 2000;41(8):1315-17.

12.Weinmann P, Moretti JL. Metoclopramide has no effect on abdominal activityof sestamibi in myocardial SPECT. Nucl Med Commun. 1999;20:623-25.

13.Hofman M, McKay J, Nandurkar D. Efficacy of milk versus water to reduce interfering infra-cardiac activity in Tc-99m sestamibi myocardial perfusion scintigraphy. Nucl Med Commun. 2006;27(11):83-42.

14.Purbhoo K, Vangu W. Efficacy of full-fat milk and diluted lemon juice in reducing infra-cardiac activity of (99m)Tc sestamibi during myocardial perfusion imaging. Cardiovasc J Afr. 2015;26(4):171-76.

15.Malek H, Hedayati R, Yaghoobi N, Bitarafan-Rajabi A, Firoozabadi SH, Rastgou F. The effect of milk, water and lemon juice on various subdiaphragmatic activity-related artifacts in myocardial perfusion imaging. Res Cardiovasc Med. 2015;4(4):29235.

16.Peace RA, Lloyd JJ. The effect of imaging time, radiopharmaceutical, full fat milkand water on interfering extracardiac activity in myocardial perfusion singlephoton emission computed tomography. Nucl Med Commun. 2005;26(1):17-24.

17.Cherng SC, Chen YH, Lee MS, Yang SP, Huang WS, Cheng CY. Acceleration of hepatobiliary excretion by lemon juice on 99mTc-tetrofosmin cardiac SPECT. Nucl Med Commun. 2006;27(11):859-64.