

The Effect of Milk, Water and Lemon Juice on Various Subdiaphragmatic Activity-Related Artifacts in Myocardial Perfusion Imaging

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Background: Subdiaphragmatic activity can produce subdiaphragmatic-related artifacts, which can degrade the quality of myocardial perfusion imaging (MPI).

Objectives: We examined the impact of drinking milk, water, and lemon juice on different subdiaphragmatic-related artifacts by using ^{99m}Tc-sestamibi myocardial single-photon emission computed tomography (SPECT) in order to determine a feasible method for improving the image quality.

Patients and Methods: A total of 179 patients (age 58 ± 9.6 years) were enrolled in this study. The patients were randomly divided into five groups. Ten minutes after injection of 740 MBq ^{99m}Tc-sestamibi in both pharmacologic stress and rest phases, the individuals in group 1 were given water and milk (125 mL of each); those in group 2 were given lemon juice (250 mL); group 3 was given milk (250 mL); and group 4 was given water (250 mL), whereas no intervention was performed in group 5. The study was double-blind for both subjects and data collectors. MPI was performed for all patients and image quality was controlled by 2 experienced nuclear physicians. Interfering activity was determined visually on reconstructed images and categorized as extracardiac normalization artifact, overlapping of activity, scattering of activity, and ramp filter artifact.

Results: There were significant differences in terms of interfering activity among the five groups; group 3 (milk) had significantly lower interfering activity than other groups had, as defined by overlapping of activity (on both stress and rest images), ramp filter artifact (stress images), and scatter artifact (rest images) ($P < 0.05$). Furthermore, there was a significant difference in the incidence of good-quality images, with no interfering activity in group 3 in the resting state compared with the other groups in the study ($P < 0.05$).

Conclusions: Drinking 250 mL of milk in either the stress phase or the rest phase of imaging diminishes interfering subdiaphragmatic-related artifacts, particularly overlapping of activity in MPI SPECT, resulting in better-quality images.

Keywords: Myocardial Perfusion Imaging; Tomography; Emission Computed; Single Photon; Artifacts

1. Background

Myocardial perfusion single-photon emission computed tomography (SPECT) imaging is the most commonly performed cardiac examination in clinical nuclear medicine for the evaluation of left ventricular perfusion and function. Tetrofosmin and sestamibi, the two most frequently used ^{99m}Tc-labeled perfusion agents in myocardial perfusion imaging (MPI), are excreted through the hepatobiliary system into the duodenum and bowel. Therefore, prominent activity is frequently present in subdiaphragmatic organs in the vicinity of the heart (1-3). Subdiaphragmatic activity can be present in the liver and bowel as a result of hepatobiliary excretion of the radiopharmaceutical or in the stomach secondary to either reflux of excreted activity into the stomach or uptake of free ^{99m}Tc-pertechnetate by the gastric mucosa. Subdiaphragmatic activity can produce subdiaphragmatic-related arti-

facts, which can degrade the quality of MPI. Such artifacts typically interfere with evaluation of the adjacent inferior wall of the left ventricle (LV) and are more remarkable at the rest phase and after dipyridamole stress testing; however, they can also, rarely, interfere with assessment of the lateral wall of LV in the presence of a hiatal hernia (4, 5).

In past years, numerous different protocols have been proposed in order to seek a standard method of minimizing gastrointestinal-related artifacts and their unwanted effects-including the use of a standard meal (6), various liquids such as milk (7), milk and water (8), soda (5), milkshakes (9), and lemon juice (10), as well as the administration of different types of pharmaceuticals such as iodinated oral contrast (11), cholecystokinin (7), erythromycin (12), and metoclopramide (13, 14) with conflicting and inconclusive results (8, 11, 13-16).

2. Objectives

Although investigators have examined different substances through the years, the impact of those methods on different subdiaphragmatic-related artifacts has not been determined so far. In the present study, we endeavored to determine whether the drinking of milk, water, mixed water and milk, or lemon juice prior to MPI SPECT with ^{99m}Tc -sestamibi would diminish gastrointestinal-related artifacts as defined by overlapping, scattered activity, ramp filter, or extracardiac normalization artifacts either after pharmacologic stress testing or in the resting state in order to enhance quality of images.

3. Patients and Methods

3.1. Patient Selection

This study comprised a total of 179 patients (130 women, age 58 ± 9.6 years) who were referred to our center for MPI. The exclusion criteria for patient selection included positive history of any type of gastrointestinal, liver, or biliary system disease or surgery. To decrease the effect of stomach fullness, all patients were in fasting state for at least 4 hours before the stress phase and 2 hours before the rest phase of the study.

Patients were randomly assigned into five different groups. Ten minutes after injection of ^{99m}Tc -sestamibi in either the pharmacologic stress phase with dipyridamole (0.514 mg/kg infusion during 4 minutes) (17) or the rest phase of imaging, each patient in group 1 drank 125 mL of water and 125 mL of whole milk (nutrient content per 100 mL was total fat, 3 gr; protein, 3.3 gr; carbohydrate, 4.7 gr); each patient in group 2 drank 250 mL of diluted lemon juice (nutrient content per 250 mL was vitamin C, 60 mg; carbohydrate, 15.8 gr; fat, 0.7 gr; protein, 1 gr); each patient in group 3 drank 250 mL of whole milk; and each patient in group 4 drank 250 mL of water. The patients in group 5 were given nothing and were used as the control group. The required sample size of each group was estimated to be at least 30 patients so as to achieve an 80% power ($\beta = 0.2$) at $\alpha = 0.05$ (11). The study was double-blind for both patients and data collectors.

3.2. Acquisition Technique

MPI SPECT was performed using a 2-day stress-rest protocol, and all patients were injected with the standard dose of ^{99m}Tc -sestamibi (740 MBq) in each phase of the study. All of the images were acquired 45–60 min after injection of radiotracer. All acquisitions were performed in step-and-shoot mode by a GE DST-XLi (USA) dual-head gamma camera equipped with low-energy-high-resolution collimators. For each study, 32 thirty-sec projections were acquired with a 64×64 matrix size and a 1.33 zoom factor in a circular 180-degree arc around the patient (45-degree right anterior oblique to left posterior oblique).

All images were reconstructed by filtered back projec-

tion with a Metz filter (point spread function, full width at half-maximum of 5 and order of 8) by using a MyoSPECT application of VISION®POWER station (version 6.0.0, GE Medical Systems). No attenuation or scatter correction was applied. The rotating raw images of all of the participants were evaluated visually, and studies with motion artifacts, low-count density, or extracardiac activity related to areas other than subdiaphragmatic region (18) were excluded. Both rest and stress images were aligned at corresponding slices for comparison. The reconstructed and reoriented images were then read and analyzed visually by 2 experienced nuclear physicians, blinded to the protocol and each other's results.

3.3. Determination of the Presence and the Effect of Subdiaphragmatic Activity

The existence of radioactivity in the liver, biliary tract, bowel, or stomach in all patients was determined, and the quality of images controlled visually. The readers were blind to patients' clinical information and the liquid type that had been used. Every set of images was categorized as "good quality" when there was no interfering subdiaphragmatic activity adjacent to the LV, and "poor to suboptimal quality" when there was interfering subdiaphragmatic activity with resulting overlapping, scatter, normalization, or ramp filter artifacts or a combination of them.

3.4. Statistical Analysis

The data were described as mean \pm standard deviation (SD) and as count (%) for the interval and the categorical variables, respectively.

One sample the Kolmogorov-Smirnov test was applied in all cases in order to test for normal distribution. Statistical analyses were employed using the chi-squared test for the categorical and one-way analysis of variance with a posthoc Bonferroni correction for the numerical variables. A Kruskal-Wallis test was applied as well.

Kappa statistics were generated in order to determine the level of agreement between the two observers. A kappa value of more than 0.8 was considered to be almost-perfect agreement. The data were managed and analyzed via SPSS 15.0 for Windows, (SPSS Inc, Chicago, Illinois). A P value of less than 0.05 was considered statistically significant.

4. Results

For the study, 179 patients (130 women and 49 men) at a mean age of 58 ± 9.6 years were recruited. Table 1 shows the number of patients, age, gender, and body mass indexes of the different groups in our study, with no statistically significant difference ($P > 0.05$). Comparison of the effect of the interference activity between the groups at stress and rest conditions (Tables 2 and 3) showed that the patients in group 3 (milk) had significantly lower in-

terfering activity than the other groups had, as defined by overlap artifact (on both stress and rest images), ramp filter artifact (on stress images only), and scattered activity (on rest images only) ($P < 0.05$). Furthermore, on rest images, there was a significant difference in the incidence of good-quality images in that group of the study ($P < 0.05$).

Moreover, there was a significantly higher incidence of uninterrupted resting-state images in group 5 with no intervention compared with the other groups, leading to a repeat of the study to obtain optimal results. The agreement [kappa] rates between 2 readers in each group and each phase of the study were more than 0.8 (Table 4).

Table 1. Comparison of Clinical Characteristics between Different Groups^a

Variable	Total (n=179)	Water and Milk (n=37)	Lemon (n = 31)	Milk (n = 42)	Water (n=37)	None (n = 32)	P Value
Age, y	57.99 ± 9.6	59 ± 10	55.7 ± 9.2	58.9 ± 0.8	57 ± 8.4	56.9 ± 10.6	0.345
Gender, F/M	130/49	27/10	19/12	37/5	23/14	24/8	0.057
Body mass index, kg/m ²	28.16 ± 5.01	28.3 ± 5.7	28.5 ± 4.8	28.4 ± 4.5	27.7 ± 5.1	27.6 ± 4.9	0.917

^a Statistics are numbers or mean ± standard deviation.

Table 2. Comparison of Image Quality and Different Subdiaphragmatic-Related Artifacts in Different Groups in Stress Phase of MPI^a

Image Quality	Water and Milk (n=37)	Lemon (n = 31)	Milk (n = 42)	Water (n=37)	None (n = 32)	P Value
Good-quality images	10 (27)	5 (16.1)	15 (35.7)	11 (29.7)	7 (21.9)	0.08
Overlapping artifact	18 (48.6)	18 (58.1)	10 (23.8)	16 (43.2)	20 (62.5)	0.008
Scatter artifact	16 (43.2)	22 (71)	23 (54.8)	24 (64.9)	19 (59.4)	0.17
Ramp filter artifact	14 (37.8)	12 (38.7)	6 (14.3)	16 (43.2)	9 (28.1)	0.046
Normalization artifact	5 (13.5)	6 (19.4)	2 (4.8)	3 (8.1)	3 (9.4)	0.327

^a Statistics are No. (%).

Table 3. Comparison of Image Quality and Different Subdiaphragmatic-Related Artifacts in Different Groups in Rest Phase of Imaging^a

Image quality	Water and Milk (n=37)	Lemon (n = 31)	Milk (n = 42)	Water (n=37)	None (n = 32)	P Value
Good-quality images	10 (27)	4 (12.9)	17 (40.5)	14 (37.8)	6 (18.8)	0.049
Overlapping artifact	15 (40.5)	20 (64.5)	9 (21.4)	12 (32.4)	19 (59.4)	0.001
Scatter artifact	14 (37.8)	22 (71)	17 (40.5)	22 (59.5)	21 (65.6)	0.013
Ramp filter artifact	7 (18.9)	7 (22.6)	3 (7.1)	6 (16.2)	10 (31.3)	0.11
Normalization artifact	4 (10.8)	3 (9.7)	1 (2.4)	1 (2.7)	4 (12.5)	0.2

^a Statistics are numbers (%).

Table 4. Comparison of Kappa Values between the 2 Readers in Each Group and Each Phase of the Study

Phase of Study and Subgroups	Kappa Value	P Value
Stress	0.907	0.001
Overlapping	0.955	0.001
Scatter	0.908	0.001
Ramp filter	0.924	0.001
Normalization	0.971	0.001
Rest	0.825	0.001
Overlapping	0.855	0.001
Scatter	0.876	0.001
Ramp filter	0.926	0.001
Normalization	0.957	0.001

5. Discussion

This study showed that drinking 250 mL of milk 10 minutes after ^{99m}Tc -sestamibi injection in either the stress phase or the rest phase of MPI can cause a statistically significant difference in the amount of extracardiac subdiaphragmatic activity particularly, the overlapping artifact.

The hepatobiliary tract is the main route for the excretion of ^{99m}Tc -sestamibi (3) and potentially leads to significant extracardiac interfering activity and artifacts (4). Subdiaphragmatic-related artifacts may exert remarkable deteriorating effects on the accuracy of MPI in different ways. One of those ways is caused by scattered activity from subdiaphragmatic organs particularly on the inferior wall-resulting in normalization or decrease in the severity of the perfusion abnormality in this region. Therefore, the perfusion defect of the inferior wall may be obscured, and even if it is more pronounced at rest than at stress, it may mimic reversibility of the inferior wall. Furthermore, scattered activity can lead to large areas of decreased activity as a result of inappropriate count normalization and increased image variability. Moreover, there is the possibility of distortion of wall motion quantification.

Contrary to scattered activity, adjacent extracardiac hot areas may result in prominent diminished activity in the adjacent myocardium. This artifact is related to the reconstruction algorithm used in filtered back projection. The ramp filter is an intrinsic component of filtered back projection, and it is applied to remove the star artifact associated with reconstruction of a finite number of projection images. The ramp filter decreases count density adjacent to an intense object, better delineating its borders and increasing its contrast. Be that as it may, when the ramp filter is applied to an area of intense tracer concentration adjacent to the heart such as the liver, stomach, or bowel it may result in artifactually decreased activity adjacent to those hot objects. As a result of variation in the distribution and intensity of subdiaphragmatic activity between stress and resting images, the ramp filter artifact is variable as well. The ramp filter effect is worse when subdiaphragmatic activity is of higher intensity and the cutoff frequency is lower (4). Therefore, both scatter and ramp filter artifacts may produce fixed, reversible, or reverse-distribution inferior artifacts (19-25).

Available softwares for MPI SPECT processing typically normalize myocardial activity to the hottest pixel. When spatial limits are defined for the production of myocardial slices, the goal is to select only myocardium, eliminating any extracardiac activity. If that does not happen, an extracardiac normalization artifact may be created. It may be difficult and sometimes unavoidable to completely eliminate extracardiac activity because it would result in cropping some of the myocardium as a result of overlap artifact. Consequently, it may be necessary to rescans the patient to obtain optimal results (4).

Numerous studies have introduced many methods for

eliminating the source of artifacts and for augmenting MPI accuracy (12-22). However, no investigations have been conducted so far on the effects of different protocols on various artifacts related to gastrointestinal activity. Despite the fact that various protocols have been introduced to reduce the amount of subdiaphragmatic activity, the role of each protocol on different types of artifacts related to subdiaphragmatic activity has hitherto remained unknown.

Water, milk, soda, lemon juice, and fatty meals are different substances that investigators have tested, and they are known to change the pattern of extracardiac activity in MPI; however, there is still a paucity of data in the existing literature on the possible effects of those substances on different artifacts (12-22). Hara et al. noted that reduction of subcardiac activity can occur by drinking small amounts of soda as the result of stomach distention, drawing gastrointestinal activity away from the myocardium (5). In another study, Boz et al. showed the usefulness of stomach fullness on extracardiac activity in MPI imaging by comparing patients in fasting and non-fasting states. Hurwitz et al. showed the positive effect of drinking milk immediately after radiotracer injection as a result of gallbladder drainage (9). Cherng et al. demonstrated that lemon juice may accelerate transit of ^{99m}Tc -tetrofosmin transit from the liver and can eliminate interfering subdiaphragmatic activity (10). In a study by Peace and Lloyd, the impact of water and fatty milk on MPI was evaluated in 260 patients, and no considerable differences were found in the quantitative results. However, the authors reported the effectiveness of delayed imaging in eradicating the interfering subdiaphragmatic activity (16). Excretion of cholecystokinin may be stimulated by fatty meals and accelerate clearance of radiotracer through the hepatobiliary system. Moreover, the presence of water and food can distend the stomach. Consequently, the intestines underneath may be drawn away from the inferior wall of the left ventricle (5, 26).

Our study demonstrated that drinking 250 mL of milk 10 minutes after ^{99m}Tc -sestamibi injection in either the rest phase or the stress phase of MPI can improve image quality by decreasing subdiaphragmatic activity and, in particular, the artifacts related to overlapping of activity. As that artifact is responsible for more uninterpretable images, it is advisable that drinking of milk be conducted as a simple technique to decrease interfering subdiaphragmatic activity and to obtain good-quality images in ^{99m}Tc -sestamibi MPI SPECT.

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Authors' Contributions

Seyed Hassan Firoozabadi and Feridoon Rastgou: Data collection. Hadi Malek, Nahid Yaghoobi, Raheleh Hedaya-

ti, and Ahmad Bitarafan-Rajabi: Data collection, analysis and writing of the manuscript.

References

- Higley B, Smith FW, Smith T, Gemmell HG, Das GP, Gvozdanovic DV, et al. Technetium-99m-1, 2-bis [bis (2-ethoxyethyl) phosphino] ethane: human biodistribution, dosimetry and safety of a new myocardial perfusion imaging agent. *J of nuclear medicine: official pub, Society of Nuclear Medicine*. 1993;**34**(1):30-8.
- Wackers FJ, Berman DS, Maddahi J, Watson DD, Beller GA, Strauss HW, et al. Technetium-99m hexakis 2-methoxyisobutyl isonitrile: human biodistribution, dosimetry, safety, and preliminary comparison to thallium-201 for myocardial perfusion imaging. *J Nuclear Med Official Pub Soc Nuclear Med*. 1989;**30**(3):301-11.
- Savi A, Gerundini P, Zoli P, Maffioli L, Compierchio A, Colombo F, et al. Biodistribution of Tc-99m methoxy-isobutyl-isonitrile (MIBI) in humans. *Eur J Nucl Med*. 1989;**15**(9):597-600.
- Burrell S, MacDonald A. Artifacts and pitfalls in myocardial perfusion imaging. *J Nucl Med Technol*. 2006;**34**(4):193-211.
- Hara M, Monzen H, Futai R, Inagaki K, Shimoyama H, Morikawa M, et al. Reduction of intracardiac intestinal activity by a small amount of soda water in technetium-99m tetrofosmin myocardial perfusion scintigraphy with adenosine stress. *J Nucl Cardiol*. 2008;**15**(2):241-5.
- Boz A, Gungor F, Karayalcin B, Yildiz A. The effects of solid food in prevention of intestinal activity in Tc-99m tetrofosmin myocardial perfusion scintigraphy. *J Nucl Cardiol*. 2003;**10**(2):161-7.
- Garcia EV, Cooke CD, Van Train KF, Folks R, Peifer J, DePuey EG, et al. Technical aspects of myocardial SPECT imaging with technetium-99m sestamibi. *Am J Cardiol*. 1990;**66**(13):23E-31E.
- van Dongen AJ, van Rijk PP. Minimizing liver, bowel, and gastric activity in myocardial perfusion SPECT. *J Nucl Med*. 2000;**41**(8):1315-7.
- Hurwitz GA, Clark EM, Slomka PJ, Siddiq SK. Investigation of measures to reduce interfering abdominal activity on rest myocardial images with Tc-99m sestamibi. *Clin Nucl Med*. 1993;**18**(9):735-41.
- 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.
- Iqbal SM, Khalil ME, Lone BA, Gorski R, Blum S, Heller EN. Simple techniques to reduce bowel activity in cardiac SPECT imaging. *Nucl Med Commun*. 2004;**25**(4):355-9.
- Vorster M, Sathekge MM, Rheeder P. Erythromycin as an alternative to reduce interfering extra-cardiac activity in myocardial perfusion imaging. *Cardiovasc J Afr*. 2010;**21**(3):142-7.
- Weinmann P, Moretti JL. Metoclopramide has no effect on abdominal activity of sestamibi in myocardial SPET. *Nucl Med Commun*. 1999;**20**(7):623-5.
- Yaghoobi N, Mardanshahi A, Rastgou F, Malek H, Firouzabady SH, Rajabi AB, et al. Impact of metoclopramide on image quality in myocardial perfusion imaging. *Nucl Med Commun*. 2012;**33**(10):1053-7.
- Pinkert J, Kutzner H, Lindner C, Lopez J, Kropp J, Franke WG, editors. Reduction of artifacts related to intestinal activity in myocardial perfusion SPECT with sestamibi.; JOF NUCLEAR MEDICINE.; 1997; SOC NUCLEAR MEDICINE INC 1850 SAMUEL MORSE DR, RESTON, VA 20190-5316; p. 274.
- Peace RA, Lloyd JJ. The effect of imaging time, radiopharmaceutical, full fat milk and water on interfering extra-cardiac activity in myocardial perfusion single photon emission computed tomography. *Nucl Med Commun*. 2005;**26**(1):17-24.
- Henzlova M. J., Cerqueira M. D., Mahmarian JJ, Yao S. S. Quality Assurance Committee of the American Society of Nuclear Cardiology Stress protocols and tracers. *J Nucl Cardiol*. 2006;**13**(6):80-90.
- Malek H, Ghaedian T, Yaghoobi N, Rastgou F, Bitarafan-Rajabi A, Firoozabadi H. Focal breast uptake of 99mTc-sestamibi in a man with spindle cell lipoma. *J Nucl Cardiol*. 2012;**19**(3):618-20.
- Heller EN, DeMan P, Liu YH, Dione DP, Zabal IG, Wackers FJ, et al. Extracardiac activity complicates quantitative cardiac SPECT imaging using a simultaneous transmission-emission approach. *J Nucl Med*. 1997;**38**(12):1882-90.
- Stern S, Greenberg ID, Corne R. Effect of exercise supplementation on dipyrindamole thallium-201 image quality. *J Nucl Med*. 1991;**32**(8):1559-64.
- Zaidi H. *Quantitative analysis in nuclear medicine imaging*. New York City: Springer; 2006.
- Kojima A, Matsumoto M, Tomiguchi S, Katsuda N, Yamashita Y, Motomura N. Accurate scatter correction for transmission computed tomography using an uncollimated line array source. *Ann Nucl Med*. 2004;**18**(1):45-50.
- Changizi V, Takavar A, Babakhani A, Sohrabi M. Scatter correction for heart SPECT images using TEW method. *J Appl Clin Med Phys*. 2008;**9**(3):2767.
- Khalil ME, Brown EJ, Heller EN. Does scatter correction of cardiac SPECT improve image quality in the presence of high extracardiac activity? *J Nucl Cardiol*. 2004;**11**(4):424-32.
- Germano G, Chua T, Kiat H, Areeada JS, Berman DS. A quantitative phantom analysis of artifacts due to hepatic activity in technetium-99m myocardial perfusion SPECT studies. *J Nucl Med*. 1994;**35**(2):356-9.
- Boz A, Yildiz A, Gungor F, Karayalcin B, Erkilic M. The volume effect of the stomach on intestinal activity on same-day exercise-rest Tc-99m tetrofosmin myocardial imaging. *Clin Nucl Med*. 2001;**26**(7):622-5.