A randomized controlled study of a modified technique to reduce extra-cardiac activity in myocardial perfusion imaging

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Running Title: Reducing interfering extra-cardiac activity

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INTRODUCTION

Myocardial perfusion imaging (MPI) is a non-invasive means to provide functional information regarding myocardial perfusion and provides accurate, reliable and important results to guide patient management and treatment [1,2]. The normal bio-distribution and mode of clearance of some radiopharmaceuticals used in MPI often leads to interfering extra-cardiac activity which could affect image quality and image interpretation, especially in the region of the inferior wall of the heart [2-4]. In addition, the intensity of interfering extra-cardiac activity may lead to repeat imaging [5]. Interfering extra-cardiac activity artifacts are mostly related to activity in the abdomen, arising from the hepatobiliary and gastro-intestinal systems [5,6]. The frequency and intensity of the interfering extra-cardiac activity is affected by the patient's physiological characteristics as well as the type of test performed [2-4]. In clinical practice, the differences in interfering extra-cardiac activity between stress and rest studies may mimic ischaemia or conceal perfusion defects. Furthermore, extra-cardiac activity can cause scatter and ramp filter artifacts thus reducing the diagnostic accuracy of the test [7]. The use iterative reconstruction techniques has been recommended to minimize artifacts related to extra-cardiac activity however, the technique Is computationally intensive and does not provide consistent results [7,8]. Various other techniques or interventions have been used and reported to reduce the frequency and intensity of extra-cardiac activity with conflicting or inconsistent results [3,4,6,9-16]. The aim of this study was to investigate whether a combined intervention was more effective than a single intervention, in reducing the frequency and intensity of interfering extra-cardiac activity. It was postulated that the use of a combined intervention would have a significantly improved effect on reducing the frequency and intensity of interfering extra-cardiac activity and thus have a positive effect on the image quality.

METHODS

A randomized controlled trial was executed to compare two interventions in randomly assigned groups within a single setting. The study took place in the Nuclear Medicine department at the Steve Biko Academic Hospital (SBAH) in Pretoria, South Africa over a period of six months. The study was approved by the Ethics committee of the Faculty of the Faculty of Health Sciences of the University of Pretoria.

Study Population

A total of 263 patients who were routinely referred to the nuclear medicine department at SBAH for two day stress-rest MPI using Tc99m-sestamibi were included in the study. Of these, 230 patients were eligible and consented to participate in the study. Sample size was calculated to obtain a modest effect size of 0.4 with a power of 0.8. Interpreters were blinded to the details of the intervention and study protocol. Patients who were pregnant, younger than 18 years of age, used gastric motility agents, had biliary or gastro-intestinal surgery or hepatic impairment or did not adhere to the preparation requirements for MPI were excluded.

Randomization

Consecutive patients were randomly assigned by a computer programme into one of two study groups (group A or B) as summarized in Fig. 1.

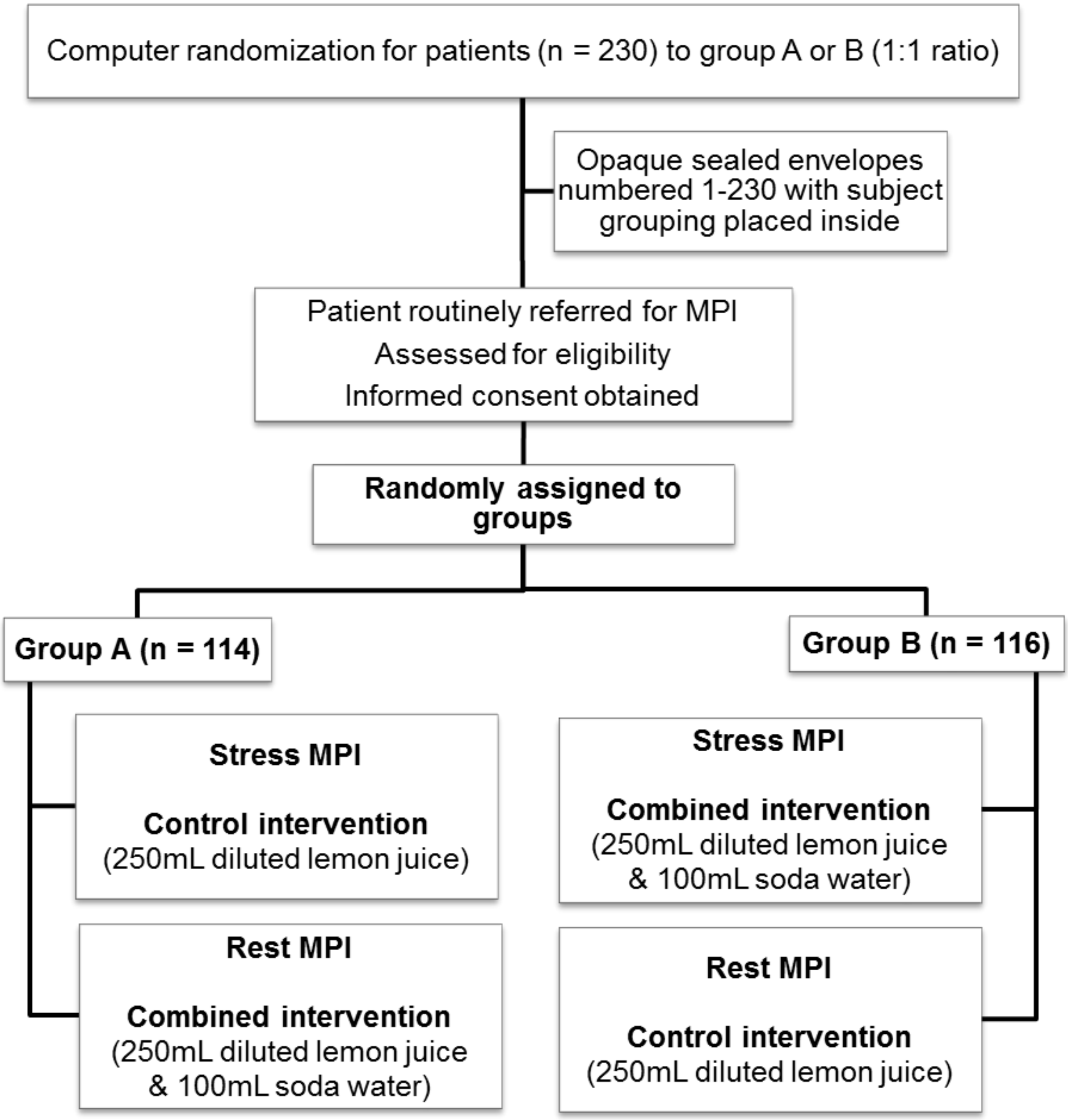

Fig. 1 The sampling and group allocation process

Study Protocol

Each patient underwent a pharmacologic or physical myocardial stress procedure according to published guidelines [17-19]. Tc99m-sestamibi was administered at maximum stress or when the target heart rate was reached during physical stress procedures. A standard dose of 555MBq (15mCi) Tc99m-sestamibi was administered for the stress and rest examinations. Patients were given the intervention required according to their group allocation. The interventions that were given included 250mL pure unsweetened, diluted lemon juice (Brookes Tru-Lem, Tiger Consumer Brands Ltd. South Africa) and/or 100mL soda water (Schweppes, Coca-cola, Amalgamated Beverage Industry, South Africa).

Acquisition

Patients were imaged in the supine position using a double-headed E-CAM (Siemens, Germany) gamma camera fitted with a low energy, high resolution collimator with the detectors configured at 90°. Prior to the patient undergoing the single photon emission computed tomography (SPECT) acquisition for diagnosis and interpretation, early static images were obtained at 50-60 minutes after injection for stress and rest imaging for three minutes per frame on a 256x256 matrix with a zoom of 1.45. This was followed by the gated SPECT acquisition using eight frames and 30 projections of 25 seconds each on a 64x64 matrix with a zoom of 1.45 leading to a pixel size of 1.6mm. A starting angle of 45° was applied with a counter clockwise rotation over 90° in step-and-shoot mode. Late static images were then obtained after the SPECT acquisition at 75-90 minutes post injection for both stress and rest examinations. The early and late static images that were used for data collection included the following: a 45° left anterior oblique projection (45° LAO), a 45° left posterior oblique projection (45° LPO) and a supine anterior (Ant) projection. Processing of the static images was performed using Siemens E-soft 4DM (Siemens, Germany) software without attenuation correction after applying a Butterworth filter. SPECT images were processed using filtered back projection. Since the SPECT images were not used for analysis in this study, the effect of the SPECT processing technique filtered back projection versus iterative reconstruction methods) on image quality was not evaluated.

The frequency of interfering extra-cardiac activity was qualitatively determined by analysis of the raw Ant, LAO and LPO planar data of the stress and rest images at both time points. Three interpreters blinded to the study protocol analyzed the images independently. In instances where the results of the two interpreters differed, the third interpreter's opinion was considered. The frequency was then recorded based on the agreement of two out of three interpreters. The intensity of interfering extra-cardiac activity on the three planar images was semi-quantitatively analyzed using the grading scale adapted from Hofman et al and Hambye [2,4]. A grading value (0-3) was assigned to the early and late rest and stress images using the scale indicated in Table 1.

Table 1. Intensity grading scale descriptors

Grade	Relative **intensity** of extra-cardiac activity compared to myocardial activity	**Effect** of extra-cardiac activity on interpretation of inferior wall	
0	Absent	**None**	Clear separation between left ventricle and digestive structures. No effect on image interpretation
1	Less than myocardium	**Mild**	Some overlap between digestive activity and left ventricle. Minimal effect on interpretation.
2	Equal to myocardium	**Moderate**	Overlap between digestive activity and left ventricle. Potential compromise of interpretation but still feasible. Study does not need to be repeated.
3	Greater than myocardium	**Severe**	Inferior cardiac wall not assessable due to interference. Study must be repeated.

Two of the three interpreters quantified the interfering extra-cardiac activity by determining the MYO:EXC ratio. The MYO:EXC ratio was quantified using the raw anterior data as well as the raw LAO data of the stress and rest imaging at both time points. On the anterior projection, a circular semi-automatic region of interest (ROI) surrounding the myocardium of the left ventricle was drawn. Adjacent to that, an irregular, manual ROI (approximately 2 pixels wide) extending inferiorly from the lateral region of the circular ROI to the medial aspect thereof was drawn. Both ROIs were copied between the stress and rest studies and onto the LAO at both time points to increase reproducibility. The mean myocardial and extra-cardiac counts were used to calculate the ratio of myocardial to extra-cardiac activity as described by Vorster and Peace and Lloyd [3,6]. Separate ratios were obtained for the stress and rest imaging at both time points for both groups. The average MYO:EXC ratio of the two interpreters was used for statistical analysis after intra-class correlations were performed.

Statistical Analysis

Data was analyzed using STATA13 statistical software (StataCorp LP, Texas, USA). A *P* value ≤ 0.05 was considered significant. Patient characteristics in the two groups were compared using the chi—squared test of association for categorical data and a 2-sample t-test for continuous data. A paired sample t-test was used to analyze the change in frequency and grading of interfering extra-cardiac activity as well as the MYO:EXC ratio between the early and delayed stress and rest studies. The MYO:EXC ratio of the control and combined intervention groups was compared using a 2-sample t-test to determine which group showed the greatest reduction in interfering extra-cardiac activity. To determine the effect of time on the MYO:EXC ratio at dual time points, the t-test was repeated for various groups and analyzed using analysis of variance (ANOVA).

RESULTS

Patient Characteristics

Patients were randomly assigned to one of two groups (group A: n = 114 or group B: n = 116). From the 263 patients referred for MPI, a total of 230 recruited patients were eligible for inclusion in this study. Allocation, follow-up and analysis of the sample is shown in Fig. 2. Group A consisted of 54 males and 41 females while there were 55 males and 45 females in group B. A *P* value less than or equal to 0.05 was considered significant. There were no significant differences between groups in terms of demographic or anthropometric data. Furthermore there were no significant differences

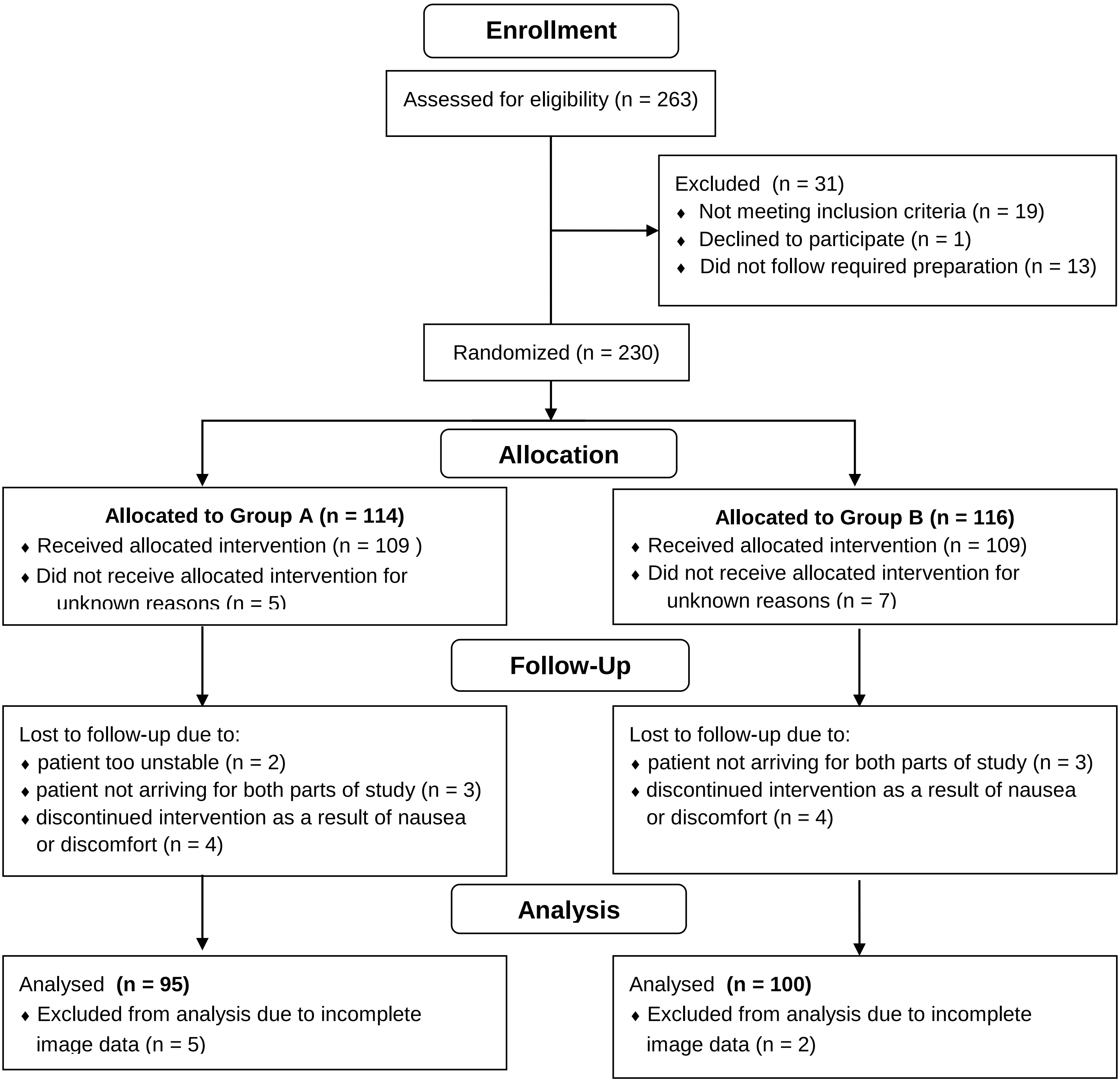

Fig. 2 Group allocation, follow-up and analysis flow chart

between groups in terms of stress method, administered dose, imaging times for early and delayed images or co-morbidities such as diabetes (*P* = 0.416), hypertension (*P* = 0.851) and dyslipidaemia (*P* = 0.426). Group characteristics are summarized in Table 2.

Table 2. Group characteristics

Variable	**Group A (n = 95)**	**Group B (n = 100)**	***P* value**
Age (years)	57.99 ± 11.93	58.80 ± 12.50	0.644
Height (m)	1.71 ± 0.09	1.70 ± 0.09	0.274
Weight (kg)	83.68 ± 21.02	83.86 ± 22.97	0.956
BMI (kg/m^2)	28.43 ± 6.29	28.89 ± 6.85	0.625
Stress Injected dose (mCi)	15.55 ± 1.29	15.25 ± 0.85	0.062
(MBq)	575.18 ± 47.63	564.25 ± 31.53	
Rest Injected dose (mCi)	15.39 ± 1.06	15.44 ± 1.31	0.792
(MBq)	569.57 ± 39.22	571 ± 48.65	
Imaging time (min):			
Early stress	55.32 ± 9.27	57.89 ± 11.80	0.093
Delayed stress	70.32 ± 9.27	72.89 ± 11.80	
Imaging time (min):			
Early rest	58.08 ± 12.87	57.16 ± 9.87	0.573
Delayed rest	73.08 ± 12.87	72.16 ± 9.87	

Interfering Extra-cardiac Activity

The frequency and average intensity of interfering extra-cardiac activity based on the agreement of two out of three interpreters are expressed in percentages and average grading scores as illustrated in Table 3.

Table 3. Frequency and intensity of interfering extra-cardiac activity between groups

	Frequency			**Average grading score**		
	Group A	**Group B**	***P***	**Group A**	**Group B**	***P* value**
Early stress	76%$^{+}$	70%*	0.366	1.07^{+}	0.85*	0.073
Early rest	69%*	72%$^{+}$	0.700	1.02*	0.92^{+}	0.417
Delayed stress	57%$^{+}$	51%*	0.416	0.72^{+}	0.61*	0.389
Delayed rest	54%*	54%$^{+}$	0.965	0.60*	0.56^{+}	0.721

* Combined intervention (250mL diluted lemon juice and 100mL soda water)

\+ Single intervention (250mL diluted lemon juice)

No significant difference in the frequency or average intensity of interfering extra-cardiac activity between groups was apparent. There was a 6% decrease in frequency when the combined intervention was given during the stress studies. However, in the rest studies there was a 3% increase in frequency when the combined intervention was given during the early imaging. There was no change in frequency during delayed imaging. Although the grading of interfering activity decreased with the combined intervention in the stress studies, it increased in the rest studies when the combined intervention was given. There was moderate agreement between interpreters in determining the frequency (κ = 0.355) and fair agreement in determining the intensity (κ = 0.248) of interfering extra-cardiac activity. The MYO:EXC ratio at the early and delayed time point for the stress and rest imaging is illustrated in Fig. 3.

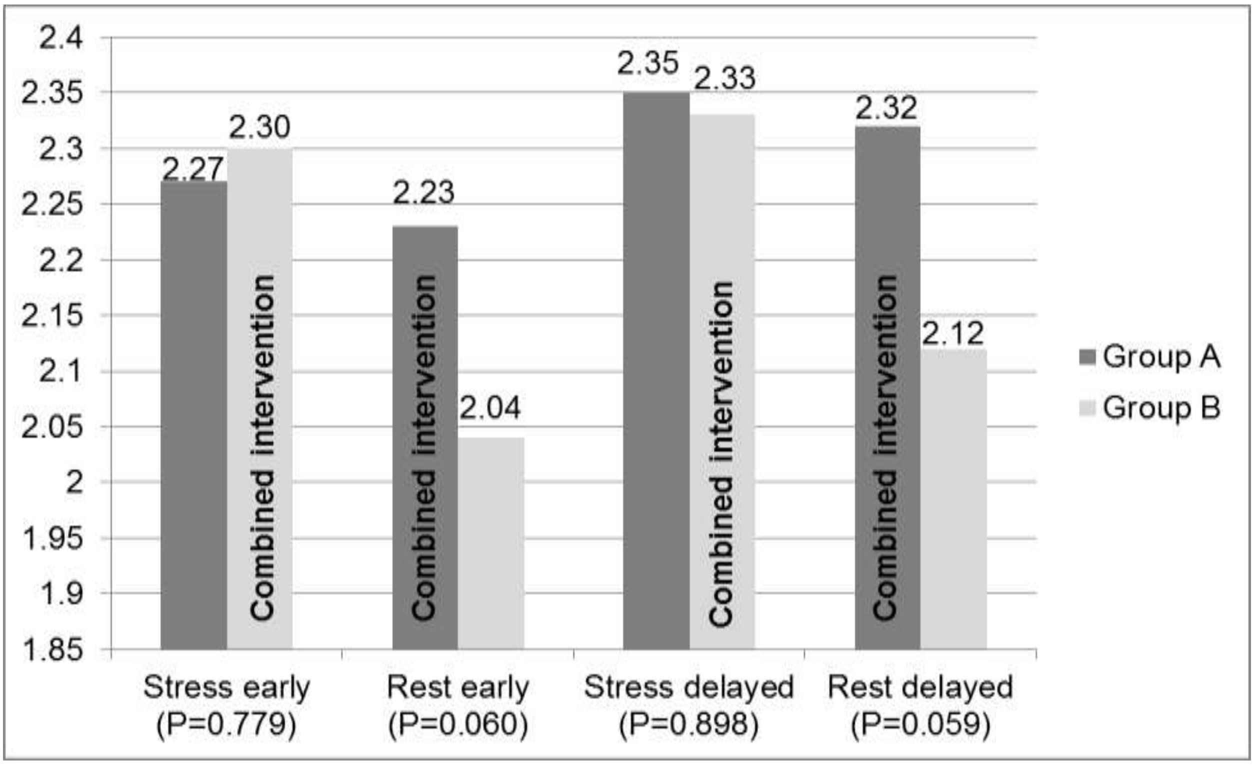

Fig. 3 Comparison of MYO:EXC ratio of early and late stress and rest examinations

Although there were no significant differences in the MYO:EXC ratio between the groups, the early and delayed rest studies were marginally not significant. Intra-class correlation indicated moderate agreement (R = 0.550) between the two interpreters in calculating the MYO:EXC ratio. The differences between the frequency and grading of interfering extra-cardiac activity as well as the MYO:EXC ratio of the early and delayed stress and rest studies is shown in Table 4.

Table 4. Effect of time on frequency and intensity of interfering extra-cardiac activity

Time point	**Mean frequency**	***P* value**	**Mean grading score**	***P* value**	**MYO:EXC ratio**	***P* value**
Early stress A	76%	<0.001**	1.07	<0.001**	2.27	<0.001**
Delayed stress A	57%		0.72		2.35	
Early rest A	69%	<0.001**	1.02	<0.001**	2.23	<0.001**
Delayed rest A	54%		0.60		2.32	
Early stress B	70%	<0.001**	0.85	<0.001**	2.30	0.218
Delayed stress B	51%		0.61		2.33	
Early rest B	72%	<0.001**	0.92	<0.001**	2.04	<0.001**
Delayed rest B	54%		0.56		2.12	

* $P \leq 0.05$ significant

**$P \leq 0.01$ highly significant

For groups A and B there was a highly significant reduction in the frequency and intensity of interfering extra-cardiac activity between the early and delayed images in the stress and rest studies. The greatest reduction in frequency (- 19%) was seen in the stress images of both groups while the greatest decrease in intensity (- 0.42) of the grading score between the early and delayed rest images of group A. There was also a highly significant difference in the MYO:EXC ratio between the early and delayed images with a 0.08 - 0.09 increase in ratio. Fig. 4 illustrates the effect of the combined intervention as well as the effect of time on the intensity of interfering extra-cardiac activity.

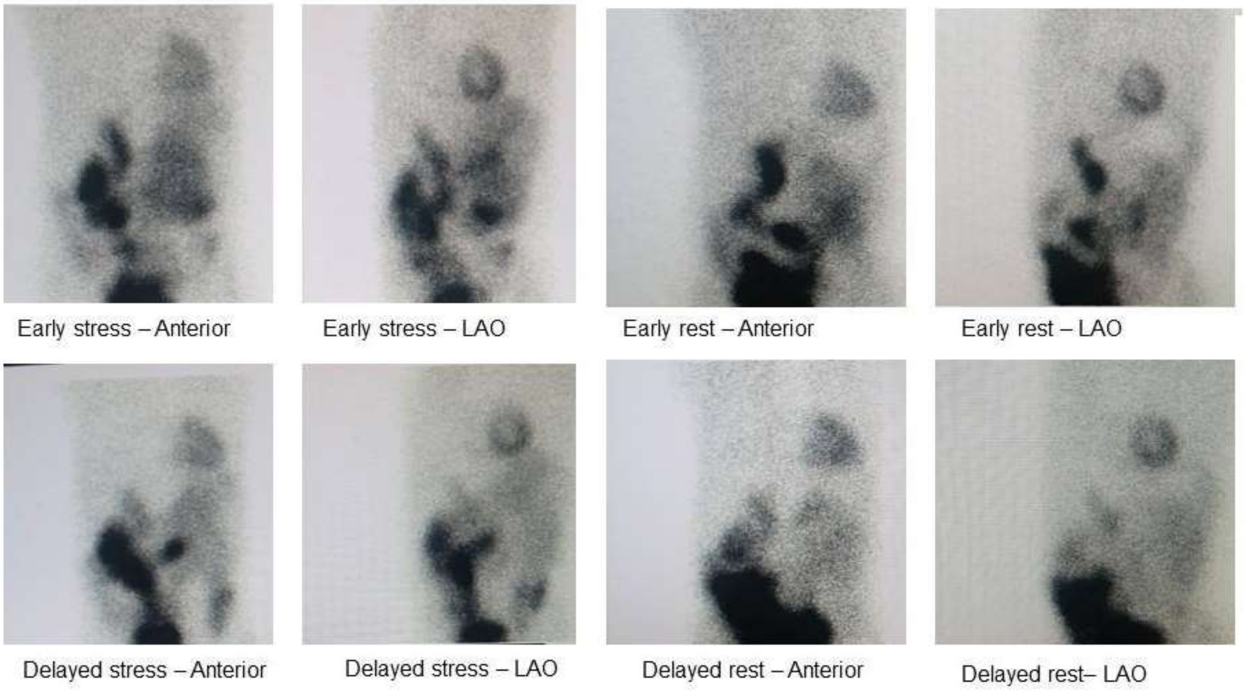

Fig. 4 Planar images from a patient in group A illustrating the effect of using a combined intervention and delayed imaging on interfering extra-cardiac activity

DISCUSSION

Artifacts resulting from extra-cardiac activity can be reduced by the application of iterative reconstruction methods during processing [7,8], the use of attenuation correction [13], or the administration of pharmacologic or meal-based substances after the radiopharmaceutical administration. Some techniques that have been reported to reduce the amount of extra-cardiac activity include:

(i) altering the standard patient position [14].

(ii) the use of substances that stimulate hepatobiliary clearance or gastric motility [6,15].

(iii) the administration of food or liquids prior to imaging in order to distend the stomach and push the bowel loops caudally and thus further from the myocardium (volume effect) [4,12,13,16,20].

(iv) delayed imaging in which physiologic clearance of the tracer is used [3,21,22].

The most common techniques used to reduce interfering extra-cardiac activity are the administration of food (cheese sandwich /chocolate bar / fatty meal) or liquids (water / full-cream milk / diluted lemon juice) to either stimulate hepatobiliary clearance or to distend the stomach [3]. Currently, there is no standard approach as to which technique(s) is most effective in reducing the interfering extra-cardiac activity. Within the local setting, the standard protocol followed was to administer 250mL diluted lemon juice after the radiopharmaceutical injection in order to stimulate hepatobiliary clearance of the radiopharmaceutical. The volume effect by use of carbonated beverages had not yet been explored.

Data from a total of 390 MIBI studies on 195 patients who were randomly assigned to one of two groups was used in this research study. Although there was no significant change of interfering extra-cardiac activity when the combined intervention was given, a decreasing trend in the frequency was noted. The highest frequency (76%) of interfering extra-cardiac activity was noted in the early stress images of the patients in group A that received the single intervention. The least frequent (51%) interfering extra-cardiac activity was noted after the combined intervention was given, in the delayed stress images of group B suggesting the improved efficacy of a combined intervention in reducing the frequency of interfering activity. Similarly, a study by Hara et al reported a frequency of 90.6% in a control group that did not receive any intervention and a significantly decreased frequency of 69.8% after 100mL of soda water was given to the experimental group immediately prior to imaging. There was less attenuation present when soda water was used as compared to other liquids or solid food. Since soda water does not stimulate hepatobiliary clearance of the radiopharmaceutical, the additional use of the Monzen position reiterates the usefulness of combined interventions to reduce interfering extra-cardiac activity [12]. A combined intervention that focussed on the volume effect was used by Boz et al. who reported a significant reduction in the frequency of interfering extra-cardiac activity in the experimental group when compared to the use of a single intervention in the control group [16]. The results are further supported by Van Dongen and van Rijk who reported the favourable outcome of a combined intervention (milk and water) over water or milk alone [13].

No significant difference in the grading of the interfering extra-cardiac activity between groups was found. The results indicate that the grading did not exceed 1.07 when the single intervention was given and 1.02 with the combined intervention. From the grading scale this implies the mild intensity of extra-cardiac activity was consistently less than the myocardial activity. The supporting description of the grading score was that there was some overlap between digestive activity and the left ventricle but the interfering activity would have minimal effect on interpretation. These findings are supported by Hofman et al and Yaghoobi et al, who reported the highest percentage of the same grade among groups of their respective studies [4,23]. The overall low grading in the current study could be attributed to the effectiveness of using lemon juice as the single intervention as reported by Cherng et al [15]. The grading of interfering activity decreased with the combined intervention in the stress studies, however it increased in the rest studies when the combined intervention was given. This inconclusive result could have been influenced by the lack of symmetry of the grading score assigned to the interfering activity between interpreters. Interpreter one consistently assigned a higher grading score for the intensity of interfering extra-cardiac activity when compared to interpreter two and three. The discrepancy in agreement between interpreters could be explained by the presence of low grade interfering activity which has been reported to make interpretation rather complex [4,11].

There was no significant difference in MYO:EXC ratio between the groups which correlates with the results of previous studies using similar methods to quantify the MYO:EXC ratio [3,6]. The MYO:EXC ratio of the early and delayed rest studies were only marginally not significant with P values of 0.060 and 0.059 respectively. There was greater improvement in the MYO:EXC ratio in the rest studies when the combined intervention was given. However, there was a small decrease of 0.03 and 0.02 in the MYO:EXC ratio in the early and delayed stress studies respectively. In a study of the effect of carbonated water prior to myocardial SPECT, Vermeltfoort et al found persistence of interfering infra-cardiac activity in some patients who consumed carbonated water [5].

Similarly to the current study, patients were asked to drink carbonated water immediately before imaging. It has been suggested that the effect of the carbon dioxide within the carbonated water is transient and decreases after eructation [5,24]. Thus, the decrease in the MYO:EXC ratio in the delayed stress studies when the combined intervention was given may have been impacted by this natural biologic process. Overall, the MYO:EXC ratio was higher than the recommended target to non-target ratio of 2:1 and was also higher than results from previous studies [3,5,6,12,15,16,20,25]. It is suspected that the differences in imaging times between the studies played a role in the discrepancies of the ratio between studies. In addition, the different methods of ROI definition, ROI placement and different interventions given may have contributed to the different MYO:EXC ratio results. As such, the differences in study designs and methods of quantifying the MYO:EXC ratio posed a challenge to accurately compare the current results to other published studies.

For both groups there was a highly significant reduction in the frequency of interfering extra-cardiac activity as well as the grading score in the delayed images. The greatest change in frequency was seen in the stress images with a 19% difference between the two time points. The grading score showed greatest reduction between the early and late rest images with a significantly increased MYO:EXC ratio between the two time points. Despite the changes in grading score and MYO:EXC not being clinically significant, the results of the current study are supported by other studies [2,3,15].

Peace and Lloyd reported a significant effect of injection to imaging time on the MYO:EXC ratio between 30 minute, one hour and two hour images [3]. The current results indicate a significant increase in the MYO:EXC ratio after a 15 minute delay. Burrel and MacDonald stated that one of the most important approaches to reducing interfering activity is to wait an adequate amount of time between radiopharmaceutical administration and imaging to allow sub-diaphragmatic activity to clear [11]. This is supported by other reports of poorer image quality and major interference of digestive activity with shorter injection to imaging times [2,26]. On the contrary, some authors have reported that increasing the time between injection and imaging has the benefit of reducing hepatic activity but it also potentially leads to reconstruction artifacts due to the increase in activity in the bowel loops [3,25].

The combined intervention that stimulates hepatic excretion of the radiopharmaceutical as well as utilising the volume effect can thus be used to overcome this challenge and facilitate improved image quality with reduced interfering extra-cardiac activity for best results with delayed imaging. Considerations for using the combined intervention include using a larger volume of soda water and using a more palatable substitute to stimulate hepatobiliary radiopharmaceutical clearance. We further recommend that the effect of combined interventions in single-day protocols be explored in terms of improving image quality and reduction of interfering extra-cardiac activity, not necessarily in terms of reduction of injection to imaging time.

LIMITATIONS

Although the results are generalizable to MPI protocols using food or liquids as interventions to reduce interfering extra-cardiac activity, the unpleasant taste of lemon juice was not tolerated well by all the patients. Alternative options to stimulate hepatobiliary clearance could be considered. The primary limitation of this study was the semi-automatic cardiac and manual extra-cardiac ROI definition. ROI definition was interpreter dependent and although ROIs were copied onto the different images of individual patients, they may have varied between patients, which may have introduced random error in calculating the MYO:EXC ratio. There were no significant differences in group allocation in terms of stress method, however, discrepancies in interfering extra-cardiac activity between various stress methods was not determined due to disproportion in the ratio of pharmacologic to physical stress. It is acknowledged that a third group receiving no intervention would have been helpful in validating the results. However, considering that the significant decrease in interfering extra-cardiac activity with the use of lemon juice (the Departments standard protocol) has been reported [6,15], the addition of the third group was considered unethical.

CONCLUSION

There were no statistically or clinically significant differences in frequency or intensity of interfering extra-cardiac activity when a combined intervention was used. However, the combined intervention did show potential to decrease the frequency and grading of interfering activity with greater effectiveness in the stress studies. The use of a combined intervention to stimulate hepatic excretion of the radiopharmaceutical while at the same utilising the volume effect to push the bowel loops away from the inferior wall of the myocardium is advantageous in MPI especially when used with delayed imaging.

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