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Abstract

Purpose: Gated single-photon emission computed tomography (SPECT) imaging of myocardium by Technetium-99m (^{99m}Tc) and Thallium-201 (^{201}Tl) is used extensively to measure quantitative cardiac functional parameters. But factors affecting normal values for myocardial functional parameters and population specific standards have not yet been established. The aim of the study was to determine the effect of sex, radiotracer, rotation angles and frame rates on resting myocardial wall thickening (WT) and to develop a Japanese standard of normal values for WT. **Methods:** Data from a total of 202 patients with low possibility of having cardiac problems were collected from 9 hospitals throughout Japan. Patients were divided into 5 groups according to study protocol, and WT was evaluated according to 17-segment and 4-region (basal, mid and apical regions and apex) polar map distribution. **Result:** WT was generally higher in females than in males irrespective of the use of radiotracers, rotation angles or frame rates, and the difference was highly significant in the mid and apical regions. In any protocol used, resting myocardial thickening in the apex was higher than in the mid and apical regions, thickening was lowest in the basal region, suggesting heterogeneous regional myocardial thickening (%) in normal subjects. Different rotation angles showed no significant change on WT, but different frame rates and tracers showed significant WT change in both sexes. Percent thickening of myocardium was significantly higher in imaging by ^{99m}Tc-labeled tracers than in ^{201}Tl. **Conclusion:** Sex, radiotracers and frame rates had a significant effect on myocardial thickening, and the importance of population specific standards should be emphasized. A normal database can serve as a standard for gated SPECT evaluation of myocardial thickening in a Japanese population and might be applicable to Asian populations having a similar physique.

Keywords: Quantitative gated SPECT – Regional myocardial thickening – ^{99m}Tc-sestamibi – ^{201}Tl – population specific standard

Introduction

Gated myocardial perfusion single-photon emission computed tomography (SPECT) imaging by Technetium-99m (^{99m}Tc) and Thallium-201 (^{201}Tl) is used extensively to measure quantitative cardiac functional parameters. Quantification of regional myocardial wall thickening (WT) may enhance diagnostic accuracy and reproducibility of interpretation of gated perfusion SPECT. Under many patho-physiological conditions, myocardial perfusion and thickening may be either concordant or discordant. Regional WT also varies considerably from base to apex in the same ventricle in normal subjects. As a result, quantification of regional WT may have considerable clinical importance when measuring the extent and severity of abnormal thickening [1]. Previous studies have shown significant gender and population-specific difference for normal limits of ejection fraction (EF) and volumes (end diastolic and end systolic volumes) by gated SPECT imaging with QGS(Cedars Sinai Medical Center, LA, USA). Females have shown higher EF and lower left ventricular volumes than males, even after correction for body surface area [2-4]. Considering the study populations, EF was higher and left ventricular volumes were lower in Japanese than in Americans, which may have depended on a combination of body weight, age and different population background [4]. For these reasons, gender and population specific standards for normal limits need to be established for better accuracy in interpretation of various gated myocardial SPECT parameters.

Left ventricular EF and regional myocardial WT can now be simultaneously evaluated with regional perfusion by gated myocardial perfusion SPECT [5]. Magnetic resonance imaging (MRI) is well validated for the assessment of myocardial wall motion and thickening in patients with normal and impaired ventricular function. There is high agreement between gated SPECT and MRI for both wall motion ($P<0.001$) and WT ($P<0.001$) [6]. Regional WT can be quantified reliably from the count density changes during the cardiac cycle on ECG-gated SPECT images, and the method is highly reproducible [1]. The ability to combine functional with perfusion data without alignment problems is certainly one of the major advantages of quantitative electrocardiogram (ECG)-gated SPECT over traditional methods using scintigraphy, echocardiography and left ventriculography [7]. WT calculated by ECG gated SPECT with QGS software (version 4.0) may be more useful than regional perfusion or wall motion analysis for the prediction of myocardial viability or functional recovery after coronary artery bypass grafting [8-10].

We hypothesized that normal standard for myocardial WT by gated SPECT imaging may vary depending on sex, protocols and population background, so specific standards are necessary for better interpretation of WT abnormalities. Since the backgrounds of Japanese population referred to in nuclear cardiology studies are specific, namely, higher age and higher frequency of small heart, use of standards specific for a Japanese population has been emphasized [4]. Still, a Japanese standard for normal limit of regional myocardial thickening by gated SPECT imaging has not yet been established. The aim of the study was to evaluate the effect of sex, radiotracers, frame rates and rotation angles on WT and to define the resting myocardial WT pattern in a normal Japanese population by gated myocardial SPECT. Finally, the normal limits obtained for regional myocardial thickening in a Japanese population were compared with the results of previous US studies.

Materials and methods

Study population

Data from a total of 202 patients with low possibility of having cardiac problem were collected from 9 hospitals throughout Japan. Gated SPECT with ^{99m}Tc labeled tracers were done on 59 male and 57 female patients with the mean age of 63± 14 and 59±14 years respectively. ^{201}Tl studies were done on 46 male and 40 female patients with the mean age of 61±16 and 57±19 years respectively. Mean EF was 64±6% in male and 69±7% in female using ^{99m}Tc tracers; it was 62±7% and 67±8% in male and female respectively using ^{201}Tl for gated SPECT imaging. The main source of the database was derived from the Japanese Society of Nuclear Medicine working group activity for myocardial SPECT standardization.[11] Data collection was approved by an appropriate ethical committee or a review board in each hospital. Selection criteria of subjects with a low likelihood of cardiac disease are as follows. Subjects who had taken part in exercise were included, although we analyzed only resting gated SPECT in this study. Subjects with no abnormal findings in ECG for ischemia or underlying cardiac diseases were included. Subjects with normal coronary arteriography and those who were not indicated for coronary arteriography because of low possibility of ischemic heart disease were included in this study. Subjects with hypertension and diabetes that required medication were excluded. Subjects with inappropriate arrhythmia for ECG gating were also excluded.

Gated SPECT acquisition protocols

The amount of the standard administration dose of ^{99m}Tc perfusion tracers and ^{201}Tl depended on the institutes. However, the tracer dose and SPECT acquisition parameters were confirmed in each institute, and were judged appropriate for reliable results. The data of ^{99m}Tc-hexakis- 2-methoxy-isobutyl- isonitrile (MIBI) and tetrofosmin were not separated. Either low-energy high-resolution (LEHR) or general-purpose (LEGP) collimators were used. A projection set of 360-degree (n=118) or 180-degree (n=84) rotations derived from triple-detector cameras or dual-detector cameras with a rectangular or 76-degree configuration was used. For gated acquisition, division of R-R interval was 16 (n=69) or 10 (n=47) frames for ^{99m}Tc tracers, while it was 16 (n=37) or 8 (n=49) frames for ^{201}Tl studies. The acquisition angle for each projection was 4-6 degrees per step. Matrix size was 64X64. No attenuation correction method was used in any of the hospitals.

Data transfer and reconstruction

The gated SPECT projection data were transferred by the original or DICOM format to Kanazawa University. The data format was modified, if necessary, to the appropriate format for further processing. Reconstruction of SPECT images was done by a Butterworth pre-filter and a ramp filter using the same reconstruction parameters for both ^{99m}Tc and ^{201}Tl studies. The order of the Butterworth filter was 8 and the cut-off frequency was 0.40 cycles/cm. QGS software was used to generate gated SPECT quantification parameters including regional WT [12]. Automatic processing was used in principle, and some manual modifications were done if necessary.

Statistical analysis

Data analysis was done using a computer-based program, 'The Statistical Discovery Software', JMP IN, version 5.1.2. Patients were divided into 5 groups according to study protocol, and resting myocardial wall thickening (WT) was evaluated based on 17-segment [13] and 4-region (basal, mid and apical regions and apex) polar map distribution. The parameters were written as mean ± standard deviation. The differences in segmental values were calculated by ANOVA test. A p value of less than 0.05 was considered significant.

Results

Mean segmental values for resting WT were calculated based on 17-segment and 4-region polar map distribution in gated perfusion SPECT images. Table 1, 2 and 3 show the mean WT values for 17 segments with P values for sex, frame rates, rotations and tracer differences. In normal subjects, WT was generally higher in females than in males irrespective of the use of radiotracers, rotation angles or frame rates, and the difference was highly significant in the mid and apical regions (Table 4). Segmental WT values are relatively constant in each of the basal, mid and apical regions (Fig. 1), so we used 4 standard values for basal, mid, apical regions and the apex. In all protocols used, regional myocardial thickening in the apex was higher than in the mid and apical regions, thickening was lowest in the basal region, suggesting heterogeneous regional myocardial thickening (%) in normal subjects (Table 4). Rotation angles showed no significant effect on WT (Table 3 and 5), except in the mid region in the 360-degree rotation method for ^{99m}Tc at 16-frame protocol where WT was significantly higher in mid-anterior segments in both sexes. The frame rate had a significant effect on WT for both ^{99m}Tc and ^{201}Tl gated SPECT. WT was generally higher in 16 frames than in 10 frames in ^{99m}Tc gated SPECT protocols irrespective of rotation angle; the difference was significant in the mid and apical regions in females and in all 4 regions in males (Table 5, Fig. 2). WT was also slightly higher in 16 frames than in 8 frames in ^{201}Tl gated SPECT protocols, and the difference was significant in the mid region in females and in the basal region in males. Depending on radiotracers, percent thickening of myocardium was significantly higher in imaging by ^{99m}Tc labeled tracers than ^{201}Tl in mid and apical regions in both sexes and also in the apex in males (Table 5, Fig. 3).

Discussion

Mean segmental values for resting myocardial WT in 202 Japanese subjects with low possibility of having cardiac problem were calculated by gated SPECT with QGS based on 17-segment and 4-region polar map distribution. Resting WT was generally higher in females than in males irrespective of the use of radiotracers, rotation angles or frame rates, and the difference was highly significant in the mid and apical segments. Different rotation angles showed no significant change on WT, but different frame rates and tracers showed a significant effect on WT in both sexes.

Regional differences

Segmental WT values were relatively constant in each of the basal, mid and apical regions, so we used 4 standard values for basal, mid, apical regions and the apex. Irrespective of protocol used, the regional myocardial thickening in the apex was higher than in the mid and apical regions, thickening was lowest in the basal region, suggesting heterogeneous percent myocardial thickening in normal subjects, which is consistent with previous post-stress ^{99m}Tc-sestamibi gated SPECT studies [1, 14-16]. This study further confirms the heterogeneity of regional WT in gated SPECT imaging at rest as well and also in studies using different protocols and radiotracers.

Gender difference

In this study, resting WT was generally higher in females than in males in all protocols and the difference was highly significant in the mid and apical regions (Table 4). So far we know, there is no published report with regard to the sex difference of regional WT, so we could not strictly compare our findings of higher regional WT values in females irrespective of gated SPECT protocols and radiotracers. One of the protocols used in this study (resting gated SPECT imaging by ^{99m}Tc tracers with 360 degree rotation and 10-frame) is partially comparable to the protocol used in previous studies in a US population (post-stress gated SPECT imaging by ^{99m}Tc-sestamibi with 180 degree rotation and 8-frame), where the average WT values (F, 48.9±11.7%, M, 43.0±9.8%; mean ± SD) were more or less similar to that of combined values by Germano et al. (M+F, 43 ± 17%) [12] and Sharir et al. (M+F, 46 ± 20%) [16], but the average WT values (F, 57.7 ± 10.5,M, 51.7 ± 10.4 %) in a similar protocol with 16-frame were higher with significant gender difference as well. Percent WT values were different between male and female in the study by Shirakawa et al. in a Japanese population [14]. We thus recommend gender specific normal database for better evaluation of regional WT abnormalities.

Effect of protocol and tracer

Major SPECT technology and preference may differ among countries. About half of the SPECT acquisition is performed with 360-degree rotation in Japan, but 180-degree rotation is more commonly used in the USA. Though, different rotation angles showed no significant difference for measuring wall thickening, frame rate had a significant effect on WT for both ^{99m}Tc and ^{201}Tl gated SPECT in this study. WT was generally higher in the higher frame rate protocols irrespective of tracers and rotation angles; the difference was significant in mid and apical regions in both sexes and also in the apex in males. Using same radiotracer, the lower frame-rate (8-frame) used in previous studies on a US population [1, 12, 14] and also in this study (10-frame) showed lower WT values than that of higher frame-rate (16-frame) protocols. In this study, percent thickening of myocardium was higher in imaging by ^{99m}Tc labeled tracers than in ^{201}Tl, which can be explained from the intrinsic difference in image resolution between these two tracers, which may create problems, especially in small hearts, to delineate left ventricular cavity in ^{201}Tl images [17]. Thus, normal standard specific for the protocol used is essential for better interpretation of regional WT by quantitative gated SPECT imaging.

Need for standards for specific population

Dependency of normal limits of cardiac functional parameters on the sex, radioisotope and protocol is important [18], and also the background of patients referred to in nuclear cardiology studies may vary between races. Thus, establishing normal values for specific nationalities or races is necessary for accurate quantification [4]. Important criteria of a Japanese population referred to in nuclear cardiology studies include a high incidence of a small heart and a relatively advanced age. Changes in matrix size or in the filter cut-off frequency significantly influence the results of quantitative gated SPECT in small hearts, and a smaller pixel size and /or a sharper filter have been suggested to enhance accurate interpretation [19, 20]. Some institutes in Japan prefer ^{201}Tl studies to ^{99m}Tc-labeled tracers. Considering the diversity of preferences in gated SPECT imaging, normal standards for specific populations and imaging techniques should be created and used for proper management of cardiac problems. Although we have analyzed WT in a Japanese population, dependency on gender, radioisotopes and framing rate would be applicable to other populations as well.

Recommended normal values

Normal values for resting myocardial WT in the Japanese population varied depending on protocol and radiotracer. Higher frame rates and ^{99m}Tc labeled tracers showed higher WT values in both sexes. For the protocols using ^{99m}Tc with 180 or 360-degree rotations and 16 frames (Fig. 1), regional mean WT values for basal, mid, apical regions and apex are 25.0%, 53.1%. 69.0% and 77.4% in females and 24.4%, 46.9%, 62.4% and 73.7% in males. If the mean – 2 SD is tentatively used for the lower limit of WT, the threshold values for basal, mid, apical regions and apex are 5%, 34%, 46% and 55% for females, and 4%, 29%, 42% and 52% for males. An appropriate threshold, namely, whether mean -2SD is applicable to all clinical studies, should be further validated. As ^{99m}Tc with 10 frames and ^{201}Tl with 16 frames using 360 degrees rotation protocols showed similar WT values, the average of the mean regional WT values may be used for these protocols. In that case, the regional WT values are 24.8%, 47.9%, 59.7% and 67.2% in females and 22.6%, 39.9%, 51.7% and 61.5% in males for basal, mid, apical regions and apex respectively. These normal values may be used as a standard to evaluate regional WT by gated SPECT imaging in a Japanese populations and might be applicable to Asian populations having similar physique.

Conclusion

Normal regional WT by gated myocardial perfusion SPECT in a Japanese population varied significantly depending on sex, tracers and frame rates, and the importance of population specific standards should be emphasized. Quantitative assessment of regional WT by gated SPECT can be performed with better accuracy using these normal values for a Japanese population. A large clinical validation study is indicated to determine appropriate threshold values for reasonable interpretation of WT abnormalities.

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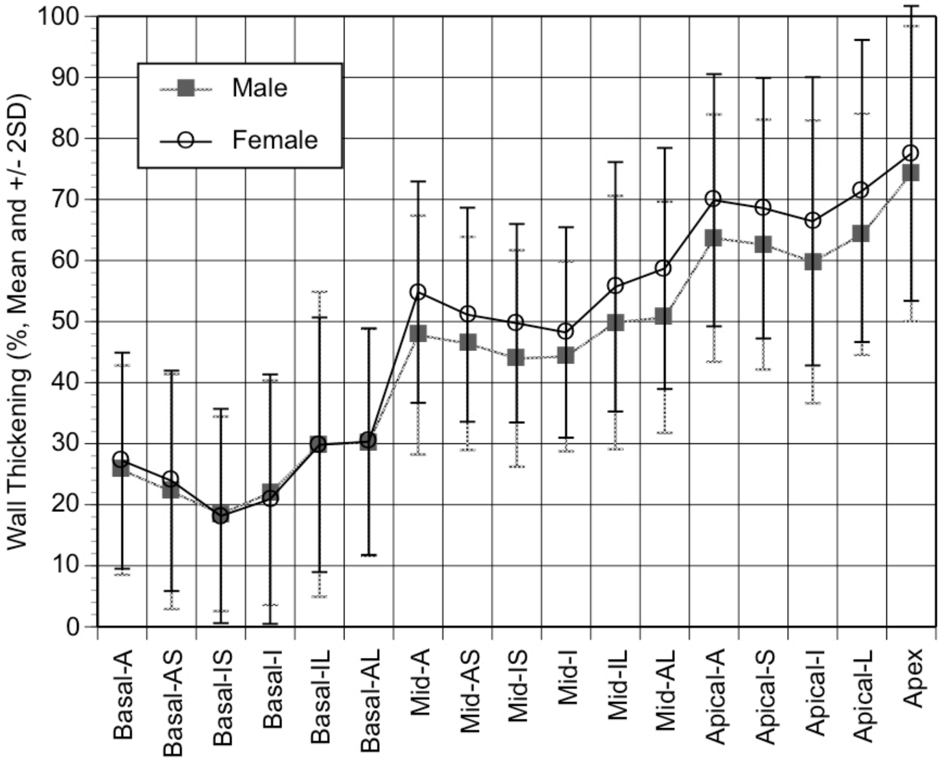

Fig. 1

Segmental myocardial wall thickening (%, mean ± 2SD) in polar map distribution using ^{99m}Tc-MIBI/Tetrofosmin and 16-frame protocol. As rotation angles showed no significant effect on WT, both 180- and 360-degree rotation data were added in this figure. Thickness increases from the basal segments towards the apical segments and is higher in females than males.

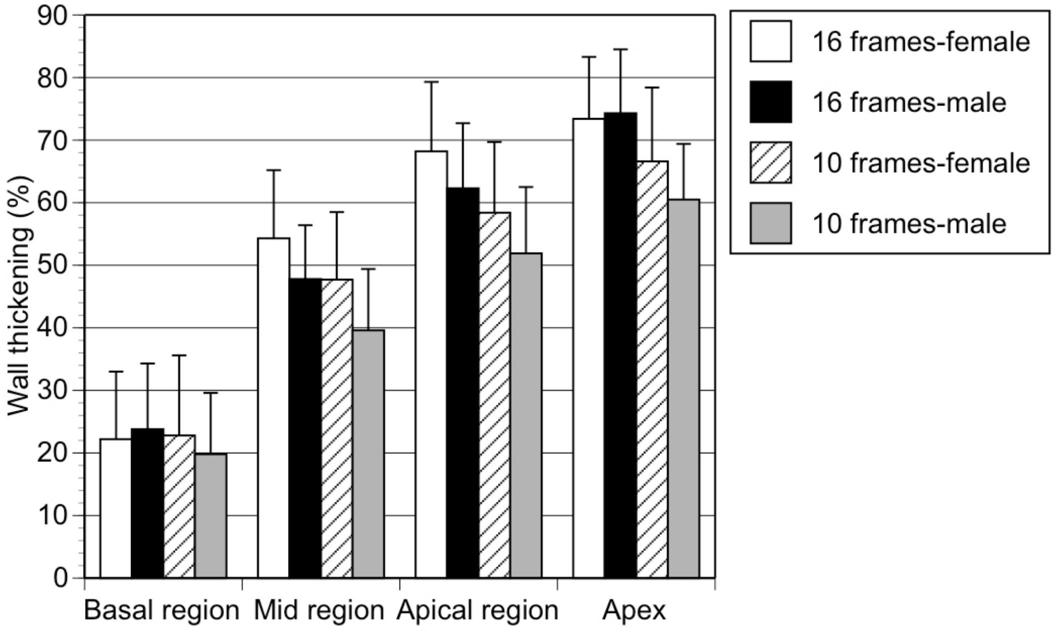

Fig. 2

Regional myocardial wall thickening (%) in ^{99m}Tc and 360-degree protocols. Thickness increases from the basal region towards the apical region and is higher in 16 frames than in 10 frames. Bars indicate + 1 SD.

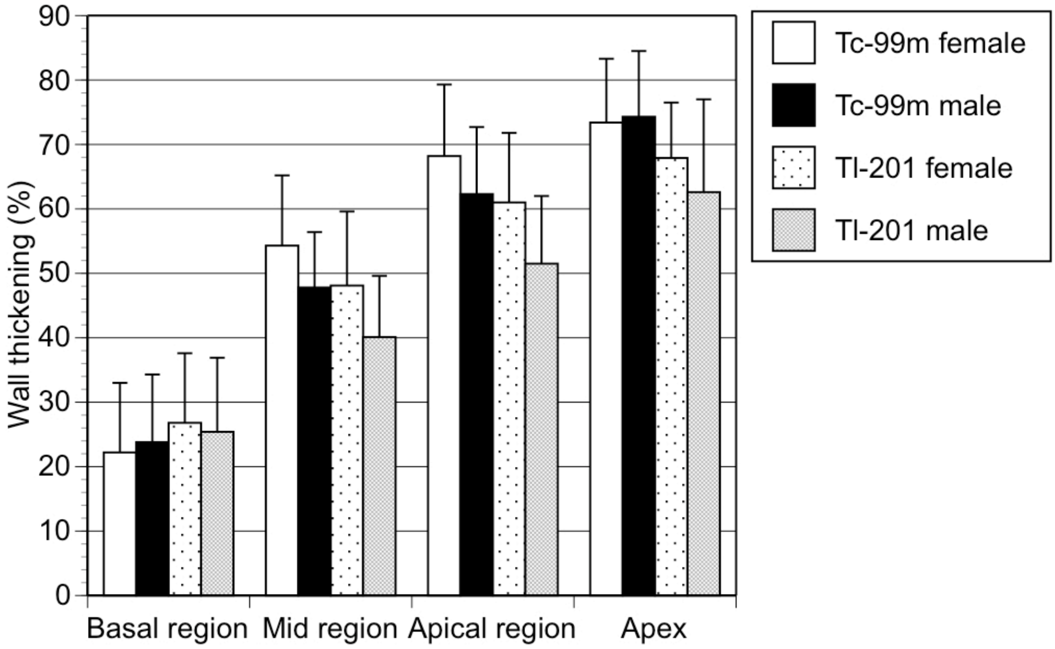

Fig. 3

Effect of radiotracers on myocardial wall thickening (WT). ^{99m}Tc showed higher WT than ^{201}Tl in gated SPECT with 16-frame protocols. Bars indicate + 1 SD.

Table 1. Segmental myocardial thickening (mean values, %) in polar map distribution by 99mTc-MIBI/Tetrofosmin gated SPECT with 360-dgreee rotation

Segments	10-frame protocol		16-frame protocol		P values			
	Female (n=24)	Male (n=23)	Female (n=16)	Male (n=18)	Female vs male		16 vs 10 frames	
					10 frames	16 frames	Female	Male
Basal A	26	22	24	25	ns	ns	ns	ns
AS	20	16	22	19	ns	ns	ns	ns
IS	14	12	15	16	ns	ns	ns	ns(0.060)
S	20	18	17	21	ns	ns	ns	ns
IL	28	26	26	31	ns	ns	ns	ns
AL	30	25	28	32	ns	ns	ns	0.027
Mid A	51	44	57	50	0.014	0.026	ns	0.018
AS	46	41	51	46	ns(0.090)	0.039	ns	ns(0.069)
IS	43	35	49	42	0.004	0.010	0.049	0.005
S	43	32	49	44	<0.0001	ns(0.092)	ns	<0.0001
IL	50	42	57	52	0.003	ns	0.035	0.002
AL	53	44	63	54	0.003	0.007	0.003	0.002
Apical A	59	53	71	64	ns	ns(0.066)	0.005	0.001
S	60	55	67	61	ns(0.092)	ns(0.067)	ns(0.051)	0.034
I	55	48	62	57	0.017	ns	0.035	0.007
L	60	52	73	66	0.009	ns(0.093)	0.0003	<0.0001
Apex	67	60	73	74	ns(0.052)	ns	ns(0.065)	<0.0001

Abbreviations: A, anterior; AS, anteroseptal; IS, inferoseptal; S, septal; IL, inferolateral; AL, anterolateral; I, inferior; L, lateral; ns, not significant.

$P < 0.05$ is significant

Table 2. Segmental myocardial thickening (mean values, %) in ^{99m}Tc and ^{201}Tl SPECT using 360-degree rotation and 16-frame protocol.

Segments	^{99m}Tc-MIBI/ Tetrofosmin		^{201}Tl		P values		
	Female (n=16)	Male (n=18)	Female (n=15)	Male (n=22)	Female vs male ^{201}Tl	^{99m}Tc vs ^{201}Tl Female	^{99m}Tc vs ^{201}Tl Male
Basal A	24	25	31	27	ns	0.047	ns
AS	22	19	24	21	ns	ns	ns
IS	15	16	19	18	ns	ns	ns
S	17	21	20	21	ns	ns	ns
IL	26	31	31	33	ns	ns	ns
AL	28	32	36	32	ns	0.037	ns
Mid A	57	50	50	41	0.007	ns(0.053)	0.003
AS	51	46	48	40	0.024	ns	ns(0.059)
IS	49	42	42	38	ns	0.029	ns
S	49	44	38	37	ns	0.001	0.008
IL	57	52	53	43	0.008	ns	0.002
AL	63	54	57	42	<0.0001	ns	<0.0001
Apical A	71	64	61	53	0.019	0.011	0.0004
S	67	61	62	50	0.004	ns	0.0007
I	62	57	57	49	0.027	ns	0.031
L	73	66	65	54	0.009	0.045	0.001
Apex	73	74	68	63	ns	ns	0.006

Abbreviations are the same as Table 1.

Table 3. Wall thickening (mean values, %) difference between 180 and 360-degree rotation in ^{99m}Tc-gated SPECT with 16-frame protocol

Segments	180-degree		360-degree		P values			
	Female (n=17)	Male (n=18)	Female (n=16)	Male (n=18)	Female vs male		180 vs 360-degree	
					180-deg.	360-deg.	Female	Male
Basal A	30	26	24	25	ns	ns	ns(0.066)	ns
AS	25	26	22	19	ns	ns	ns	0.023
IS	21	21	15	16	ns	ns	0.048	ns(0.071)
I	24	23	17	21	ns	ns	0.036	ns
IL	33	29	26	31	ns	ns	ns(0.070)	ns
AL	33	29	28	32	ns	ns	ns	ns
Mid A	53	46	57	50	0.037	0.026	ns	ns
AS	51	47	51	46	ns	0.039	ns	ns
IS	50	46	49	42	ns	0.010	ns	ns
I	48	45	49	44	ns	ns(0.092)	ns	ns
IL	54	48	57	52	ns	ns	ns	ns
AL	55	47	63	54	0.021	0.007	0.014	0.031
Apical A	69	63	71	64	ns	ns(0.066)	ns	ns
S	70	64	67	61	ns	ns(0.067)	ns	ns
I	71	63	62	57	0.044	ns	0.020	ns
L	70	62	73	66	0.047	ns(0.093)	ns	ns
Apex	81	74	73	74	ns	ns	ns(0.052)	ns

Abbreviations are the same as Table 1.

Table 4: Gender difference of regional myocardial thickening (%) by gated SPECT protocols.

Protocols	Patients		Regional myocardial thickening (%)			
	Gender	Number	Basal	Mid	Apical	Apex
Tc-180-16F	Female	17	27.7 ±9.2	51.8 ±8.4	69.9 ±11.6	81.5 ±12.9
	Male	18	25.1 ± 10.0	45.9 ±9.7	62.5 ±10.1	73.2 ±11.8
	P value		0.046	<0.0001	<0.0001	ns(0.054)
Tc-360-10F	Female	24	22.8 ±12.8	47.7±0.8	58.4 ±11.3	66.6 ±11.8
	Male	23	19.8 ±9.8	39.7 ±9.8	51.9 ±10.6	60.5 ±8.9
	P value		0.026	<0.0001	<0.0001	ns(0.052)
Tc-360-16F	Female	16	22.2 ±10.8	54.3±10.9	68.2 ±11.1	73.4 ±9.9
	Male	18	23.8 ±10.5	47.8 ±8.6	62.3 ±10.4	74.3 ±10.2
	P value		ns	<0.0001	0.001	ns
Tl-180-8F	Female	25	25.3±12.0	43.5 ±12.7	57.8 ±11.7	64.4 ±12.8
	Male	24	22.7 ±8.3	39.4 ±8.3	49.8 ±10.0	58.5 ±12.0
	P value		0.026	0.001	<0.0001	ns
Tl-360-16F	Female	15	26.8 ±10.8	48.1 ±11.5	61.0 ±10.8	67.9 ±8.6
	Male	22	25.4 ±11.5	40.1 ±9.5	51.6 ±10.5	62.6 ±14.4
	P value		ns	<0.0001	<0.0001	ns

Data expressed as mean ± SD.

Abbreviations: Tc, ^{99m}Technetium; Tl, ^{201}Thallium; F, Frame rate; ns, not significant. P values derived from ANOVA test, P < 0.05 is significant

Table 5: Effect of rotation angles, frame rates and radiotracers on regional myocardial wall thickening (WT).

Regions		Basal	Mid	Apical	Apex
Effect of rotation angles on WT					
180 vs 360-degree (^{99m}Tc and16 frames)	Female	0.0001	ns (0.068)	ns	ns (0.052)
	Male	ns	ns	ns	ns
Effect of frame rates on WT					
10 vs 16 frames (^{99m}Tc and 360 degree)	Female	ns	<0.0001	<0.0001	ns (0.065)
	Male	0.002	<0.0001	<0.0001	<0.0001
Effect of radiotracers on WT					
^{99m}Tc vs ^{201}Tl (360 and 16 frames)	Female	0.004	0.0002	0.0004	ns
	Male	ns	<0.0001	<0.0001	0.006

Data shown as P values from ANOVA test, $P < 0.05$ is significant

Abbreviations: WT, wall thickening; ns, not significant