

Early and delayed Tc-99m-tetrofosmin myocardial SPECT in patients with left bundle branch block

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To determine the utility of the myocardial tracer Tc-99m-tetrofosmin in the examination of patients with left bundle branch block (LBBB) and to investigate Tc-99m-tetrofosmin uptake and retention in the myocardium, early and delayed Tc-99m-tetrofosmin SPECT was performed in 10 patients having LBBB without coronary stenosis. *Methods:* After 740 MBq of Tc-99m-tetrofosmin injection in the resting state, the early and delayed SPECT imaging was done at 30 min and 180 min, respectively. *Results:* Decreased Tc-99m-tetrofosmin uptake in the septal segments was observed in 4 patients (40%) at 30 min and in 9 (90%) at 180 min. Reverse redistribution was seen in 9 of 10 patients. In patients with LBBB, the septal-to-lateral uptake ratio was lower in the delayed images than in the early images (0.80 ± 0.09 vs. 0.89 ± 0.09 , $p < 0.001$). In patients with LBBB, the washout rate of Tc-99m-tetrofosmin was higher in the septal segments than in the lateral segments ($28.3 \pm 4.3\%$ vs. $22.8 \pm 3.3\%$, $p < 0.001$). *Conclusion:* The SPECT data indicate that in LBBB without coronary stenosis, the uptake of Tc-99m-tetrofosmin is decreased in the septal wall, and that reverse redistribution occurs frequently. Our results contribute to the elucidation of both the cellular biokinetics of Tc-99m-tetrofosmin in the myocardium and the hemodynamics of the septum in LBBB, and indicate the possible clinical utility of Tc-99m-tetrofosmin.

Key words: Tc-99m-tetrofosmin, left bundle branch block, septum, reverse redistribution

INTRODUCTION

ALTHOUGH thallium-201 single photon emission computed tomography (TI-201 SPECT) has been widely used for the diagnosis of coronary artery disease, its use in patients with left bundle branch block (LBBB) has been disappointing because we frequently encounter decreased uptake in the septum of patients with angiographically normal coronary arteries.¹⁻⁶ Various theories have been proposed for the false positive results thus obtained, such as small vessel disease that cannot be visualized angiographically, functional ischemia caused by asynchronous contraction, and fibrodegenerative change in

the septum.^{1,7,8} The precise mechanism, however, remains unknown. There may be a limit to the use of TI-201 SPECT in the diagnosis of coronary artery disease in patients with LBBB.

Tc-99m-labeled tetrofosmin is a newly developed myocardial tracer with many advantages.⁹⁻¹¹ This tracer was reported to be rapidly cleared from the blood after intravenous administration and taken up by the myocardium and other tissues. It has been thought that once Tc-99m-tetrofosmin is taken up by the myocardium, its clearance is relatively slow, and that the redistribution does not occur for several hours.^{12,13} At our facilities, we do not use the ordinary protocol based on previous investigations regarding Tc-99m-tetrofosmin biokinetics; all Tc-99m-tetrofosmin SPECT data are acquired twice (30 min and 180 min after injection).

The present study was undertaken to investigate the septal uptake and retention of Tc-99m-tetrofosmin on the early and delayed images in patients with LBBB.

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METHODS

Subjects

LBBB group: Ten patients with LBBB (6 males and 4 females, aged 54 ± 10 years) were enrolled. Nine patients were asymptomatic, and one had atypical chest pain. No patient had heart disease such as coronary artery disease, cardiomyopathy, myocarditis, aortic valvular disease or hypertensive heart disease, with which LBBB is usually associated. All patients underwent coronary angiography, which disclosed normal coronary arteries.

Control group: Ten subjects were selected for the control group (7 males and 3 females, age 53 ± 11 years). Because of atypical chest pain or relatively trivial ECG findings, they had been transferred first to our radionuclide facility to rule out ischemic heart disease, but exercise myocardial

scintigrams with Tc-99m-tetrofosmin demonstrated no abnormal lesion. Coronary angiography was done in 6 subjects and showed normal coronary arteries. The average age of control group was not significantly different from that of the LBBB group.

Data Acquisition

In each patient, 740 MBq of Tc-99m-tetrofosmin was intravenously injected at rest. Immediately after the injection, each patient drank a glass of milk to accelerate the tracer clearance from the hepatobiliary system. Data acquisition for SPECT imaging was performed twice; for early imaging at 30 min and for delayed imaging at 180 min after the Tc-99m-tetrofosmin injection, with a rotating digital gamma camera equipped with a low-energy, high-resolution, parallel-hole collimator. Projection images were obtained for 30 sec each at 6° increments over 180° circular orbits starting at the 45° left posterior oblique projection and ending at the 45° right anterior oblique projection.

An exercise Thallium-201 perfusion study was performed within 4 weeks of the Tc-99m-tetrofosmin study. All patients underwent bicycle exercise according to a standard multi-stage exercise protocol, with continuous monitoring of the heart rate, blood pressure, ECG and symptoms. At peak exercise, 111 MBq of Tl-201 was intravenously injected, and the patient continued to exercise for an additional 1 minute. Data acquisition was carried out 10 min and 180 min after the ^{201}Tl administration. SPECT images were obtained, with the same data acquisition as for Tc-99m-tetrofosmin except for the data acquisition time (40 sec per frame).

Image Analysis

After data acquisition, the projection data were stored on a hard disk. After a preprocessing with a Butterworth filter, transverse axial tomograms of 5.3 mm thickness per slice were reconstructed with a Shepp-Logan filter without correction for attenuation or scatter. Data were reoriented

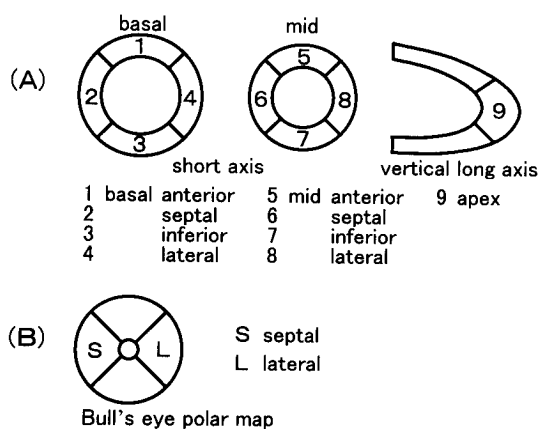


Fig. 1 (A) Two short-axis images at the basal and mid-levels and a mid-ventricular vertical long-axis image were selected for visual interpretation. 1 = basal anterior, 2 = basal septal, 3 = basal inferior, 4 = basal lateral, 5 = mid-anterior, 6 = mid-septal, 7 = mid-inferior, 8 = mid-lateral, 9 = apical. (B) Septal (S) and lateral (L) regions of interest superimposed on the bull's-eye polar coordinate map. The septal to lateral uptake ratios were determined from these regions.

Table 1 Tc-99m-tetrofosmin SPECT images of LBBB patients

Patient #	Age (y.o.)	Sex	Decreased septal uptake		Septal to lateral uptake ratio		Washout rate (%)		
			30 min	180 min	30 min	180 min	septal	lateral	
1	M.S.	63	F	+	+	0.84	0.73	33.4	27.0
2	H.M.	55	M	-	+	0.88	0.71	32.3	24.4
3	Y.Y.	74	M	-	+	0.96	0.89	23.8	18.5
4	Y.S.	57	M	+	+	0.82	0.71	30.9	24.5
5	K.K.	50	F	-	+	0.93	0.87	29.1	26.4
6	T.Y.	34	M	-	+	0.91	0.80	22.6	17.2
7	Y.T.	46	M	-	-	0.97	0.97	21.7	20.1
8	S.S.	51	F	+	+	0.80	0.74	32.5	21.1
9	A.H.	52	F	+	+	0.86	0.81	28.2	24.2
10	E.Y.	55	M	-	+	0.89	0.81	31.5	25.6
mean \pm SD		54 \pm 10				0.89 \pm 0.09	0.80 \pm 0.09	28.3 \pm 4.3	22.8 \pm 3.3

to obtain the oblique angle tomograms parallel to the long-axis and short-axis of the left ventricle.

The left ventricular myocardium was divided into nine segments: basal anterior, basal septal, basal inferior, basal lateral, mid-anterior, mid-septal, mid-inferior, mid-lateral and apical (Fig. 1A). The uptake of the tracer in each segment was scored by two experienced observers who had no knowledge of the patient's clinical information, with a four-point grading system (3 = normal, 2 = mildly reduced, 1 = moderately reduced, and 0 = defect). A segment was assessed as abnormal when the early or delayed score was ≤ 2 . Redistribution was defined as a segment with a score increase on the delayed images. Similarly, reverse redistribution was defined as a segment showing a score decrease on the delayed images.

To verify our visual impression of the septal uptake of Tc-99m-tetrofosmin, the septal-to-lateral uptake ratio on the bull's-eye polar map was quantified (Fig. 1B). After correction for the physical decay of Tc-99m, the washout rate of Tc-99m-tetrofosmin on the bull's-eye polar map between 30-min and 180-min was also calculated for the

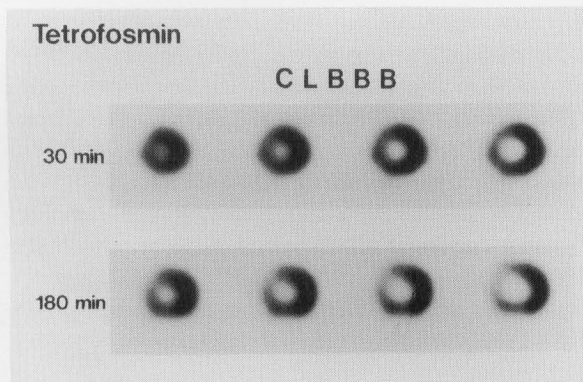


Fig. 2 Short-axis myocardial images of Tc-99m-tetrofosmin in a 57-year-old male (#4) with LBBB. On the 30 min images, decreased uptake is observed in the septal region, and this decreased uptake is more extensive on the 180 min images.

septum and lateral wall, with the formula: washout rate (%) = (counts on 30-min image - counts on 180-min image)/counts on 30-min image \times 100.

Statistical Analysis

Data are presented as the mean \pm standard deviation. The differences in the count ratio and the washout rate were compared by a paired or unpaired t-test. Statistical significance was defined as $p < 0.05$.

RESULTS

Tc-99m-tetrofosmin studies

Of the 10 patients with LBBB, 4 (40%) had decreased tracer uptake in the basal and/or mid-septal segments on the early Tc-99m-tetrofosmin SPECT images. Of the other 6 patients showing no decrease on the early image, 5 disclosed a decrease in septal segments on the delayed image. Nine patients (90%) showed a septal decrease on the delayed images (Table 1). Reverse redistribution in the septal walls was observed in 9 (90%) of 10 patients (Fig. 2). Only one patient had no septal decrease on the early or delayed images. One patient (#1) showed a decrease in not only septal but also apical segments on both the early and delayed images. In the control group, no significant decrease was observed in any segment on the early or delayed images (Table 2).

The septal-to-lateral uptake ratio in the early images was lower in patients with LBBB than in control subjects (0.89 ± 0.09 vs. 0.96 ± 0.04 , $p < 0.005$). The septal-to-lateral uptake ratio in the delayed images was lower in patients with LBBB than in control subjects (0.80 ± 0.09 vs. 0.96 ± 0.05 , $p < 0.0001$). In patients with LBBB, the septal-to-lateral uptake ratio was lower in the delayed images than in the early images (0.80 ± 0.09 vs. 0.89 ± 0.09 , $p < 0.001$) (Tables 1 and 2, Fig. 3).

The washout rate of Tc-99m-tetrofosmin in the septal segments was higher in patients with LBBB than in control subjects ($28.3 \pm 4.3\%$ vs. $23.6 \pm 4.2\%$, $p < 0.05$).

Table 2 Tc-99m-tetrofosmin SPECT images of the control subjects

Patient #	Age (y.o.)	Sex	Septal to lateral uptake ratio		Washout rate (%)		
			30 min	180 min	septal	lateral	
1	M.B.	72	M	1.01	0.97	25.3	23.3
2	T.T.	58	M	0.95	0.98	19.8	23.1
3	M.T.	39	M	0.99	1.02	14.0	17.2
4	U.H.	55	F	0.93	0.85	26.5	22.0
5	Y.Y.	61	M	0.96	0.92	27.5	25.1
6	M.M.	43	M	0.96	0.96	27.5	27.9
7	S.S.	63	M	0.96	0.92	26.2	23.1
8	T.M.	54	F	0.91	1.01	22.7	28.4
9	A.Y.	49	M	0.92	0.95	23.1	29.4
10	T.H.	38	F	1.01	1.00	22.8	21.9
mean \pm SD		53 \pm 11		0.96 \pm 0.04	0.96 \pm 0.05	23.6 \pm 4.2	24.2 \pm 3.8

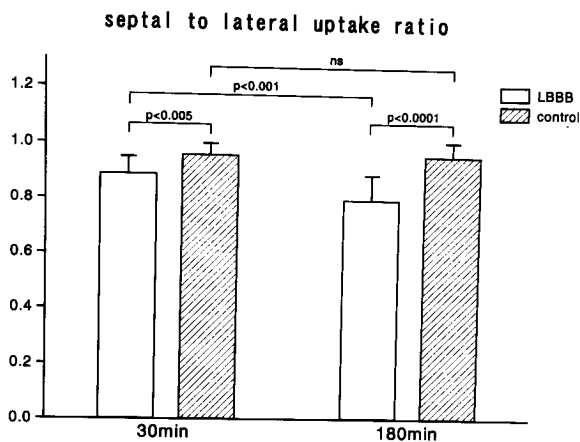


Fig. 3 Comparison of septal to lateral uptake ratio on the early (30 min) and delayed (180 min) SPECT images.

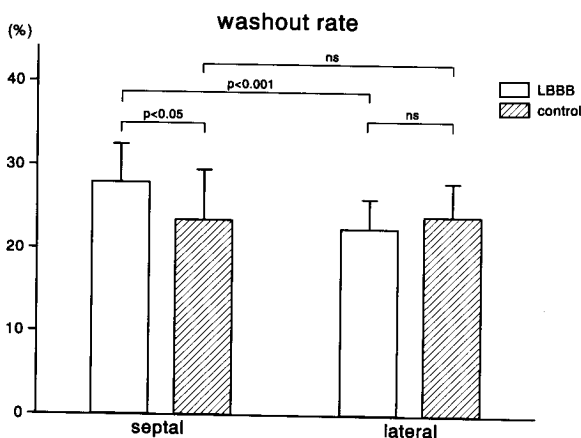


Fig. 4 Washout rate in the septum and the lateral wall.

In patients with LBBB, the washout rate of Tc-99m-tetrofosmin was higher in the septal segments than in the lateral segments ($28.3 \pm 4.3\%$ vs. $22.8 \pm 3.3\%$, $p < 0.001$). The washout rate in the lateral segments was similar in patients with LBBB and control subjects ($22.8 \pm 3.3\%$ vs. $24.2 \pm 3.8\%$) (Tables 1 and 2, Fig. 4).

Thallium-201 studies

In the exercise study with Tl-201, of the 10 patients with LBBB, 8 (80%) had decreased uptake in the basal and/or mid-septal segments on the early images. Incomplete or complete redistribution was observed in 6 of these 8 patients (75%).

DISCUSSION

Tc-99m-tetrofosmin SPECT

Tl-201 cardiac imaging has been widely used to evaluate myocardial perfusion and tissue viability in patients with coronary artery disease. Although its value as a diagnostic and prognostic test has been well established, Tl-201 is not ideal for imaging due to its low-energy photons and its

long half-life. To circumvent these limitations and to obtain better image quality and radiation dosimetry than those provided by Tl-201 scintigraphy, several Tc-99m-labeled myocardial agents have recently been proposed for myocardial blood flow studies. Tc-99m-labeled tetrofosmin is one of these newly developed agents without the disadvantages of Tl-201. Tc-99m-tetrofosmin also has potential advantages over the available myocardial tracers. The preparation is easy and fast with the use of a kit or syringe product,¹¹ and the hepatic influences in imaging are not stronger than the other Tc-99m myocardial tracers such as Tc-99m-sestamibi.

After intravenous administration, Tc-99m-tetrofosmin is rapidly cleared from the blood and taken up by the heart, muscle, liver, spleen, kidney and so on in proportion to the blood flow. The myocardial uptake is rapid but the retention is stable in contrast to the rapid blood and hepatic clearance. These favorable properties have prompted the clinical use of Tc-99m-tetrofosmin as a myocardial imaging agent.¹¹ Although the uptake to myocardium is mainly dependent on the blood flow, the precise mechanism of the entry of this tracer into myocytes has not been elucidated. The results of a recent study with isolated rat heart suggested that the uptake by myocytes is not achieved by cation channel transport, as it is for Tl-201, but rather by a metabolism-dependent process. The most likely uptake mechanism is thought to be by potential driven diffusion on the lipophilic cations across the sarcolemmal and mitochondrial membranes.^{14,15} Once Tc-99m-tetrofosmin is taken up by the myocardium, it is retained there for a relative long time. No evidence of the myocardial redistribution of Tc-99m-tetrofosmin in 3 to 4 hours was reported in normal myocardium or in patients with reversibly ischemic regions.¹²

Tl-201 SPECT in LBBB

LBBB is usually associated with diseases such as coronary artery disease,¹⁶ hypertensive heart disease,¹⁷ dilated cardiomyopathy, myocarditis¹⁸ and aortic valvular disease.^{19,20} The conduction system in the septum is easily affected by an impaired blood flow or a change in intramyocardial pressure, because the beginning of the left bundle is located in the outflow tract of the left ventricle and surrounded by tough connective tissue. Pathohistological studies have disclosed various changes resulting from LBBB such as fibrosis, cellular infiltration, vacuolation and fatty infiltration.⁸ The first investigation of LBBB with radioactive tracers was done in 1976 by McGown et al.,²¹ who demonstrated that the uptake of potassium-43 and Rubidium-81 administered at rest decreased in the antero-septal regions regardless of the presence or absence of coronary stenosis. The same findings were obtained by Tl-201 myocardial scintigraphy with its intravenous injection during exercise. Many authors have reported that even in the absence of coronary artery stenosis, a decrease in Tl-201 uptake was seen in the

antero-septal region on the early images and redistribution was observed on the delayed images.¹⁻⁶ Of the 10 patients with LBBB, 8 showed a septal decrease in Tl-201 despite having normal coronary arteries, as has been shown in previous reports. This finding of "false positivity," however, is disadvantageous in the differentiation of coronary artery disease with angiographically visible stenosis in patients with LBBB. In this respect, a pharmacologic stress test with dipyridamole, adenosine or dobutamine was reported to be more specific than exercise scintigraphy in the diagnosis of coronary artery stenosis.²²⁻²⁵

The reason why the septal decrease occurs in patients with LBBB without coronary stenosis is still unsolved, despite the many investigations of LBBB by means of Tl-201 scintigraphy. An experimental study by Hirzel et al. on dogs indicated that septal blood flow measured by radioactive microspheres was decreased by right ventricular pacing in accompanied by reduced Tl-201 activity, and from this observation they concluded that the septal decrease in Tl-201 observed in LBBB reflects functional ischemia due to asynchronous septal contractions.¹ This view that the septal decrease in Tl-201 does not necessarily indicate "genuine" ischemia was supported by the findings of Ono et al.,²⁶ who electrically induced LBBB in dogs by right ventricular pacing and reported that the reduced uptake of both Tl-201 and F-18-deoxyglucose in the septal region was accompanied by a decrease in systolic thickening and an increase in intramyocardial pressure in the diastolic phase. No lactate production was found, and the left anterior descending coronary flow was not changed, nor was the mean aortic pressure. They suggested that LBBB causes the impairment of hemodynamics in the septal wall of the left ventricle, which may result in reduced myocardial perfusion and glucose uptake.

Tc-99m-tetrofosmin SPECT in LBBB

The present report is the first on LBBB examined with Tc-99m-tetrofosmin. The results demonstrated that, similarly to Tl-201 injected during exercise, Tc-99m-tetrofosmin injection at rest is uptaken less in the septal wall of patients with LBBB. The mechanism of this septal decrease in Tc-99m-tetrofosmin is unclear, but in the same way as for Tl-201, the hemodynamic impairments which occurred in the septal wall, such as asynchronous contraction, a decrease in systolic thickening or intramyocardial pressure increase in the diastolic phase could play an important role in a decrease in regional blood flow to the septum and in a reduction in Tc-99m-tetrofosmin diffusion across the sarcolemmal and mitochondrial membrane. A septal decrease in Tl-201 was shown in 8 of the 10 patients, whereas only 4 of the 10 patients had a septal decrease with Tc-99m-tetrofosmin on the early images. This difference may be due to the situation of the tracer administration: Tl-201 injected during exercise versus

Tc-99m-tetrofosmin at rest.

Reverse redistribution of Tc-99m-tetrofosmin

The myocardial clearance of Tc-99m-tetrofosmin is relatively slow, and it has been estimated that redistribution does not occur for up to 4 hours after injection, even in reversibly ischemic segments.¹² Since this property is clinically attractive for detecting regional perfusion abnormalities in patients with acute coronary syndrome among other disorders, new protocol administering the tracers twice (e.g., the first dose during exercise, the second at rest) has been proposed.¹⁰ This idea is based on the finding by several investigations that there is an insignificant redistribution of the tracer within the first several hours after injection. In our study, however, reverse redistribution was clearly observed in LBBB patients within 3 hours. The cause of the reverse redistribution that occurred in the present LBBB patients is not known. Regarding the mechanism of the uptake of Tc-99m-tetrofosmin by myocytes, Platts et al.¹⁴ and Younes et al.¹⁵ reported that the Tc-99m-tetrofosmin accumulation by the mitochondria of myocytes is related to the ability of this tracer to transduce metabolic energy into electron-negative membrane potential. Considering this experimental result, we could speculate that in LBBB the ability of this tracer to transduce metabolic energy into membrane potential is impaired for some undefined reasons, causing relatively rapid clearance of Tc-99m-tetrofosmin from the septal wall.

CONCLUSION

In conclusion, our protocol with two SPECT imagings after the intravenous injection of Tc-99m-tetrofosmin in the resting state disclosed that in patients having LBBB without coronary artery stenosis, the Tc-99m-tetrofosmin uptake was decreased in the septum, and that reverse redistribution occurred frequently, even after 180 min. These data contribute to the elucidation of the cellular biokinetics of Tc-99m-tetrofosmin and the hemodynamics of the septum in LBBB, and suggest the clinical utility of Tc-99m-tetrofosmin.

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