Thallium-201 SPECT in Coronary Artery Disease Patients with Left Bundle Branch Block

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Fourteen patients with left bundle branch block (LBBB) underwent immediate postexercise and 3-hr delayed ^{201}Tl single photon emission computed tomography (SPECT) with quantitative analysis using bullseye polar maps. Test performance in detecting individual coronary artery stenosis ≥50% demonstrated 100% sensitivity. Specificity was 100% for circumflex stenosis, 78% for right coronary stenosis, but only 10% for left anterior descending coronary stenosis. This very low specificity was due to the fact that 3/4 (75%) patients with left anterior descending stenosis and also 9/10 (90%) patients with normal left anterior descending coronary arteries had immediate septal perfusion defects with redistribution in all cases at 3 hr. Septal abnormalities were most marked in patients who achieved high peak heart rates (>170 bpm). Thus, with LBBB, ^{201}Tl SPECT is indeterminate for left anterior descending coronary disease.

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Noninvasive testing to diagnose coronary artery disease has been disappointing in patients with left bundle branch block (LBBB). ST segment changes during exercise electrocardiography are indeterminate for ischemia in patients with LBBB (*1*). Both resting and exercise-induced regional septal asynergy assessed by equilibrium radionuclide angiocardiography have been reported to occur frequently with LBBB (*2*). Also, septal perfusion defects have been described in planar potassium-43 (^{43}K) and thallium-201 (^{201}Tl) studies despite the absence of angiographic coronary stenosis (*3,4*). Currently, single photon emission computed tomography (SPECT) is being increasingly used for the diagnosis and characterization of coronary artery disease. The present study was undertaken to determine the value of ^{201}Tl SPECT in diagnosing coronary disease in patients with LBBB.

METHODS

Patients and Normal Control Subjects

Fourteen patients (11 males and three females, mean age 63 ± 7 yr) with LBBB underwent thallium SPECT performed following graded treadmill exercise. Studies were performed to investigate the possibility of coronary disease as a cause of LBBB and/or chest pain. All patients had fixed LBBB. All patients underwent coronary angiography (Table 1). Of these, four had normal coronary arteries. Ten had ≥50% luminal diameter narrowing of one or more coronary arteries. However, six of these ten patients had no left anterior descending coronary disease. In addition, 36 control subjects (20 males and 16 females, mean age 41 yr) with normal intraventricular conduction and a <5% likelihood of coronary artery disease determined by Bayesian analysis of risk factors were studied.

Exercise Testing and Thallium-201 SPECT

All patients and control subjects underwent symptom-limited treadmill exercise using the Bruce protocol. All control subjects achieved >85% of maximum age-predicted heart rate. Of the 14 patients with LBBB undergoing coronary arteriography, only six achieved >85% of their maximum predicted heart rate (mean = 85 ± 14% bpm). Seven experienced typical angina.

For each ^{201}Tl SPECT study a 3.5-mCi dose was injected at peak exercise, and the patient continued exercising for one additional minute. Thirty-two planar acquisitions were performed for 40 sec each over a 180 degree arc extending from the 45° right anterior oblique to the 45° left posterior oblique projection. Images were obtained within 10 min following tracer injection, and delayed imaging was begun at 180 min. Using filtered back projection, oblique, orthogonal tomographic slices, each 6mm thick, were reconstructed parallel to

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TABLE 1
Thallium-201 SPECT Results in 14 Patients with LBBB Undergoing Coronary Angiography

		Catheterization results (% luminal diameter narrowing)			Thallium-201 SPECT			
Patient	Age/sex	LAD*	LCX†	RCA‡	ANT§	SEP¶	INF**	LAT††
1	59 M	N	N	100%	N	R‡‡	R	N
2	61 M	N	N	N	N	R	N	N
3	77 M	N	N	87%	N	R	N	N
4	67 M	100%	N	N	R	R	R	N
5	75 M	N	75%	N	R	R	N	R
6	64 M	N	N	68%	N	R	F	N
7***	66 M	N	84%	***	N	N	F	F
8	51 M	N	N	N	N	R	N¶¶	N
9	65 M	100%	N	100%	F§§	R	F	N
10	62 F	95%	N	N	R	N	N	N
11	50 F	N	N	N	N	R	R	N
12	60 M	50%	N	N	F	R	N	N
13	59 F	N	N	N	N	R	N	N
14	63 M	N	N	75%	N	R	R	N

* LAD = left anterior descending coronary artery.
† LCX = circumflex coronary artery.
‡ RCA = right coronary artery.
§ ANT = anterior.
¶ SEP = septal.
** INF = inferior.
†† LAT = lateral.
‡‡ R - defect with redistribution at 3 hr.
§§ F - fixed defect.
¶¶ N - normal.
*** Patient 7 - known inferior infarction, no injection of RCA.

the vertical and horizontal long axes and the short axis of the left ventricle.

From the oblique, short axis slices, extending from the apex to the base, a bullseye polar coordinate map was reconstructed, representing this three-dimensional tomographic data two-dimensionally. The apical and basal limits of the ventricle were defined by the operator while viewing the verticle long axis slice through the mid-portion of the ventricle. Moving a cursor along the long axis of the ventricle, the apex was selected as the first short axis 6 mm slice in which myocardium was visualized, and the base was selected as the last slice in which both inferior and lateral myocardium were visualized. The Emory method of bullseye map construction has been described previously (*5*). In brief, circumferential profiles of count density are obtained for each short axis slice in a manner similar to that used for standard quantitative analysis of planar thallium-201 images. The maximal count density in each of 40 9-degree wedges extending 360° around each short axis tomographic slice are plotted using rectangular coordinates. These profiles are then reconstructed using polar coordinates. For each short axis slice, the polar coordinate profile is positioned within a "bullseye" plot. Profiles are plotted concentrically, with the apical profile at the center of the bullseye and the basal profile at the periphery. The entire bullseye plot is color-coded with all pixels normalized to the region of highest count density (Fig. 1A).

The approximate vascular territories of the left anterior descending, circumflex, and right coronary arteries are diagramed in Figure 2. In most individuals at least the upper ⅔ of the septum is supplied by the left anterior descending.

Thallium-201 SPECT studies were interpreted independently of coronary angiography results. Perfusion abnormalities >2.5 standard deviations below mean gender-matched normal limits, involving more than 10 contiguous pixels on the immediate postexercise bullseye polar map, which demonstrated either partial or complete redistribution, were judged to represent ischemia. Abnormalities demonstrating no redistribution in 3-hr delayed images were judged to represent scar.

In the normal bullseye plot the count density of the lateral wall is slightly more intense than that of the septum. This is most likely attributable to the fact that in normal individuals the lateral wall is slightly thicker than the septum, and also due to the fact that the septum is attenuated to a greater degree in the imaging arc. In normal individuals count distribution is similar in immediate and delayed images.

To confirm our visual impression of alterations in septal perfusion, the lateral-to-septal wall count density ratio was quantified. Computer determined regions of interest were drawn over the lateral wall and septum (Fig. 3). Since the count density of the apex of the left ventricle and the very base of the left ventricle may be dependent upon operator slice selection in the Emory bullseye method, the apex and base were purposely excluded from these regions of interest. This ratio was calculated for the normal control subjects and

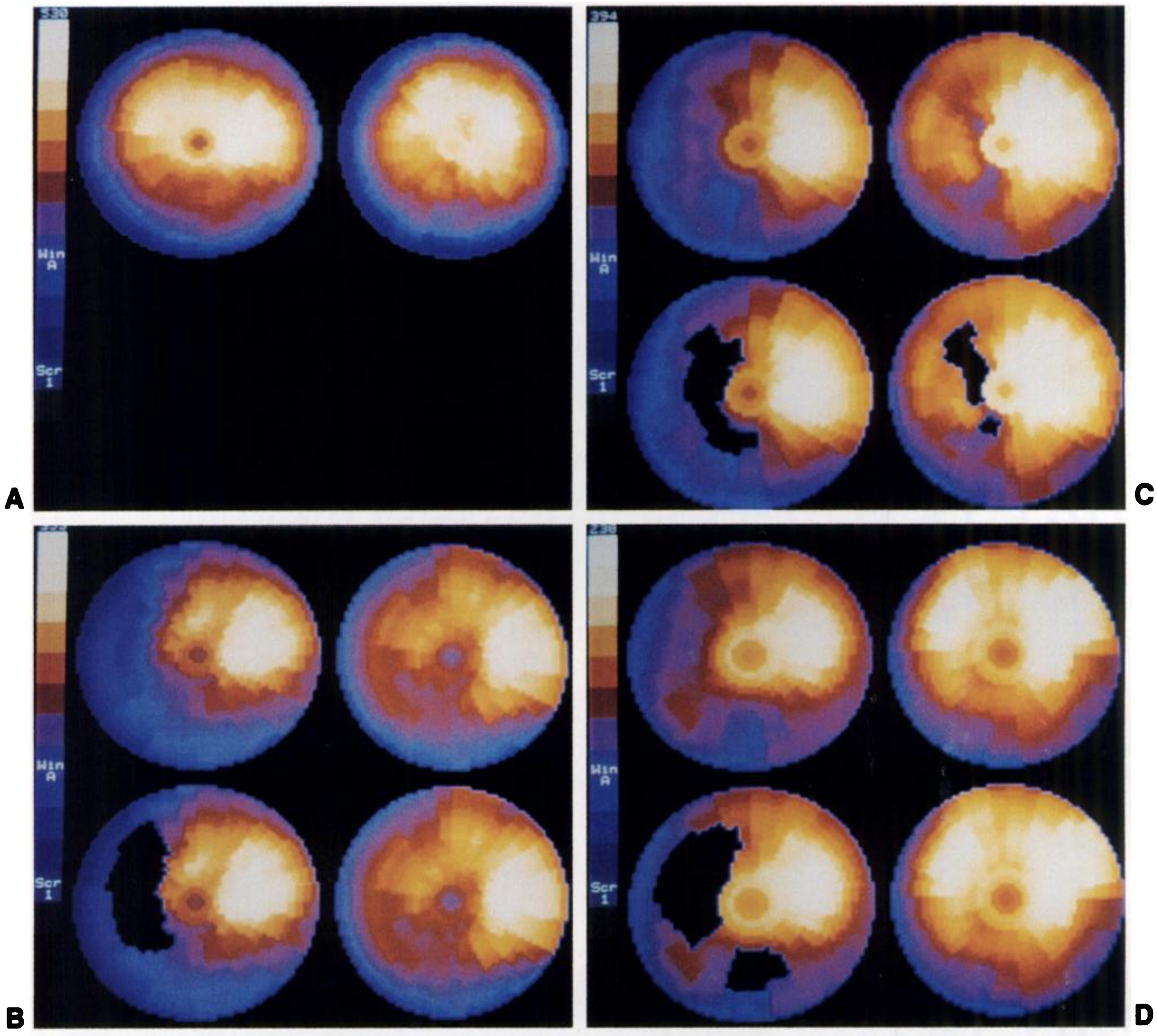

FIGURE 1
Thallium-201 SPECT bullseye images (A-D) immediately following exercise (left) and at a 3-hr delayed interval (right) are displayed. For case examples B-D, in the bottom row, comparison is made to gender-matched normal limits. All pixels > 2.5 s.d.s below mean normal limits are blackened for the immediate (left) and delayed (right) images. A: Normal study. B: Normal intraventricular conduction; left anterior descending coronary stenosis (first septal perforator branch). See text for explanation. C: LBBB; normal coronary arteries. See text for explanation. D: LBBB; normal left anterior descending coronary artery, 75% right coronary artery stenosis. See text for explanation.

the nine patients with LBBB who had neither left anterior descending or circumflex disease that could account for perfusion abnormalities in the septum or lateral wall.

To further quantify the degree of septal abnormality, a thallium "score" was generated. Within the septal region of interest, the number of standard deviations below mean gender-matched normal limits for each abnormal pixel (>2.5 s.d.s below mean normal limits) was determined. These standard deviations were then summed to generate the "score". For example, in a patient with 10 pixels each 6 s.d.s below normal, and 7 pixels each 4 s.d.s below normal within the septal region of interest, the thallium score would be $(10 \times 6) + (7 \times 4) = 88$.

With LBBB the QRS complex and thus septal asynchrony comprise a progressively greater proportion of the R-R interval as the heart rate increases. Therefore, we also correlated the lateral-to-septal count density ratio in patients with LBBB and neither left anterior descending nor right coronary artery disease with the peak heart rate achieved during exercise.

Coronary Arteriography

Coronary arteriography was performed using standard techniques. Coronary artery diameter stenosis was measured in at least two projections using digital calipers. Percent diameter stenosis was expressed as the average of these measurements.

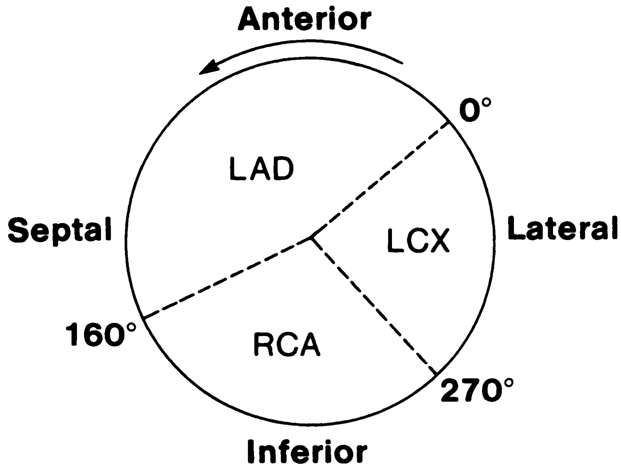

FIGURE 2
Approximate vascular territories of the left anterior descending, circumflex, and right coronary arteries superimposed upon the bullseye polar coordinate map.

Contrast arteriograms and ^{201}Tl studies were interpreted independently in a blinded fashion.

Statistics

For the patient and control groups, the lateral-to-septal count density ratios, heart rates, and thallium scores are expressed as the mean ± 1 s.d. Values for patients and control subjects were compared using the Student's t-test for unpaired data.

RESULTS

In the 14 patients with LBBB who underwent coronary angiography, the sensitivity and specificity of ^{201}Tl SPECT in identifying coronary stenosis of ≥50% luminal diameter narrowing was determined (Tables 2 and 3). For the right coronary artery all five patients with significant stenosis were identified; two studies were falsely positive for ischemia in the right coronary distribution. Circumflex coronary stenosis was correctly determined to be present in 2 of 2 patients; 12 of 12 patients without circumflex stenosis had no abnormalities in the posterolateral wall. Thus, both sensitivity and specificity for circumflex disease were 100%. Four of four patients with left anterior descending stenosis had anterior and/or septal perfusion defects for a 100% sensitivity. However, in patients with LBBB but no left anterior descending stenosis, nine of ten studies demonstrated septal perfusion abnormalities in immediate images, all of which had partial or complete redistribution in 3-hr delayed images. Thus, test specificity for left anterior descending coronary disease was only 10%.

In the 14 patients with LBBB undergoing coronary angiography, septal perfusion abnormalities were present in 12 patients. Three of these 12 patients had significant left anterior descending stenosis, but nine patients with reversible septal perfusion defects had normal left anterior descending coronary arteries. Sep-

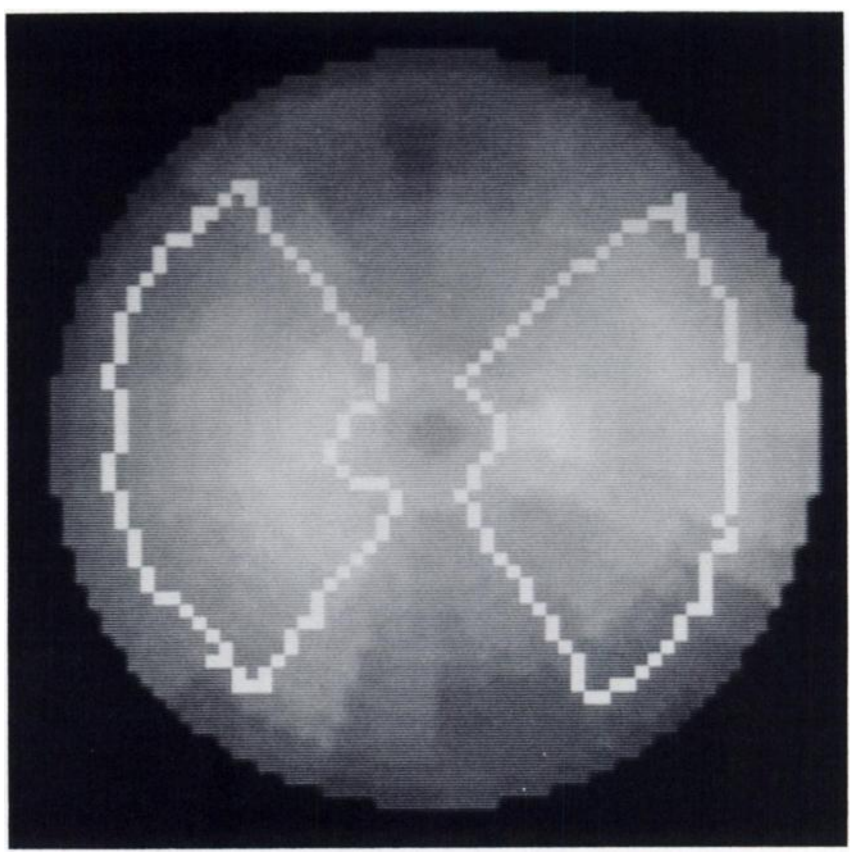

FIGURE 3
Lateral (L) and septal (S) regions of interest superimposed upon the bullseye polar coordinate map. Lateral-to-septal count density ratios are determined from these regions.

TABLE 2
Detection of Coronary Stenosis (≥50%) in 14 Patients with LBBB

	LAD*	LCX†	RCA‡
Sensitivity	4/4 (100%)	2/2 (100%)	5/5 (100%)
Specificity	1/10 (10%)	12/12 (100%)	7/9 (78%)

* LAD = left anterior descending.
† LCX = circumflex.
‡ RCA = right coronary artery.

tal perfusion defects were absent in one patient (Table 1, Patient 7) with a normal left anterior descending and in 1 patient (Table 1, Patient 10) with left anterior descending stenosis who had a reversible anterior perfusion abnormality.

By means of the computer-generated bullseye regions of interest, lateral-to-septal wall count density ratios were calculated for the nine patients with LBBB and no left anterior descending or right coronary disease, and also for the 35 control subjects (Table 3). In the normal patient population in immediate postexercise images, the lateral-to-septal count density ratio was 1.17 ± 0.08. In the 3-hr delayed images the ratio was 1.11 ± 0.08. In the normal patient population the difference between this ratio in the immediate versus delayed images was not statistically significant. In contrast, in the nine LBBB patients the lateral-to-septal wall count density ratio was 1.27 ± 0.16. This ratio is higher than that in normal individuals ($p < 0.05$). In delayed images the ratio fell to 1.13 ± 0.06, indicating significant tracer redistribution after 3 h. This ratio was not statistically different from that in normal individuals in the 3-hr delayed images. Thus, in patients with LBBB but no left anterior descending coronary artery disease, the lateral-to-septal wall count density ratio was abnormally increased, with redistribution into the septum and return to normal limits in 3-hr delayed images.

In all 14 patients with LBBB the mean thallium score in the septum was 103 ± 131 (range = 0 − 417). In patients with left anterior descending coronary disease the mean score was 140 ± 90 (range 55–265), and in those with no left anterior descending coronary disease it was 89 ± 146 (range 0 − 417).

In two patients with high peak heart rates (173 and 190 bpm) the lateral-to-septal count density ratio was markedly increased (1.63 and 1.52, respectively). These values were significantly greater than the mean ratio (1.23 ± 0.05) ($p < 0.0001$) in the patients who achieved peak heart rates <170 bpm (mean peak heart rate = 131 ± 22 bpm).

TABLE 3
Lateral/Septal Count Density Ratio in Nine Patients with Normal Coronary Arteries and 35 Control Subjects

	LBBB	NORMAL	p
Immediate	1.27 ± 0.16	1.17 ± 0.08	<0.05
4-hr delayed	1.13 ± 0.06	1.11 ± 0.08	N.S.

Case Examples

Example 1 (Fig. 1B). As a point of reference, this case illustrates the typical appearance of immediate and delayed bullseye plots in a patient with normal intraventricular conduction and left anterior descending coronary stenosis with involvement of only the first septal perforator branch. This patient was not included in the present patient series. There is markedly decreased tracer concentration throughout the septum in the immediate images with significant, nearly complete, tracer redistribution at 3 hr. The lateral-to-septal count density ratio was 1.76 in the immediate study and 1.38 in the delayed study. The septal thallium score was 236.

Example 2 (Fig. 1C). This patient, who was enrolled in the present study, had LBBB and normal coronary arteries. Similar to the previous example of a patient with left anterior descending coronary stenosis, there is markedly decreased tracer concentration in the septum in the immediate study. In the 3-hr delayed bullseye plot there is significant, nearly complete, tracer redistribution into the septum. In this case, the lateral-to-septal count density ratio was 1.52 in the immediate study and 1.25 in the delayed study. The septal thallium score was 164.

Example 3 (Fig. 1D). This patient with LBBB had a normal left anterior descending coronary artery but significant (75%) mid-right coronary artery stenosis. As noted in the previous examples, there is an immediate septal perfusion defect with significant, nearly complete redistribution at 3 hr. The lateral-to-septal count density ratio is 1.18 in the immediate study and 1.03 at 3 hr. The septal thallium score was 79. In addition, there is a moderate decrease in count density in the inferior wall of the left ventricle with significant redistribution at 3 hr, indicating ischemia in the right coronary artery distribution. Thus, this study was false positive for left anterior descending coronary disease and true positive for right coronary disease.

DISCUSSION

In patients with normal intraventricular conduction transient septal myocardial perfusion defects demonstrated by exercise thallium-201 scintigraphy are indicative of left anterior descending and/or first septal perforator coronary stenosis. Brown et al. recently reported that such reversible septal perfusion defects present in planar images were associated with poor patient prognosis and an increased risk of future cardiac events (*6*). However, the results of the present study indicate that this data cannot be extrapolated to patients with LBBB.

In patients with LBBB exercise-induced relative septal hypoperfusion has been documented by previous investigators and is supported by the results of the present study. In a study of Braat et al. among eight patients with LBBB and normal coronary arteries, in only one was a reversible septal perfusion defect present (*7*). However, Hirzel et al. studied 19 symptomatic patients with LBBB. In all 19, reversible septal perfusion defects occurred, but in only four was left anterior coronary stenosis present (*4*). Similarly, in the present study, using ^{201}Tl SPECT, we observed reversible or partially reversible septal perfusion abnormalities in 14 patients with LBBB undergoing coronary angiography, only three of whom had significant LAD stenosis. An additional ten patients with negative clinical follow-up and presumably no significant coronary disease all had reversible, exercise-induced septal perfusion abnormalities.

Thallium-201 SPECT has been demonstrated to accurately detect regional myocardial perfusion abnormalities in individual vascular territories in patients with coronary artery disease (*5*). In the detection and sizing of perfusion defects due to myocardial infarction, investigators have found SPECT to be superior to planar imaging, in part because of the higher image contrast resolution afforded by tomography (*8,9*). For detecting exercise-induced ischemia, preliminary results reported by Maddahi et al. also found SPECT to be more sensitive than planar imaging, especially for circumflex disease (*10*). Similarly, our observation of septal perfusion abnormalities in such a large percentage of patients with LBBB is also probably in part due to the improved contrast resolution and definition of individual vascular territories afforded by SPECT.

There are some advantages as well as a few potential disadvantages of analysis of tomographic images using the bullseye display. With the two-dimensional bullseye display of three-dimensional tomographic data, the perfusion pattern of the entire left ventricular myocardium is more easily assessed. Relationships between large myocardial regions such as the septum and lateral wall are more readily appreciated than by inspection of individual tomographic slices, and the extent of perfusion defects such as those in the septum associated with LBBB is better evaluated. A potential limitation is variability in the amount of myocardium encompassed by the apical-most and basal-most slices. Such impression may be due to errors associated with short axis slice selection for construction of the bullseye map. Rigorous quality control is important to assure correct slice selection. Furthermore, partial volume effect contributes to the appearance of the most apical and basal slices. With regard to analysis of septal perfusion, the base of the septum is membranous, and the length of the membranous septum among individuals is variable. This results in considerable variability in the appearance of the septum in bullseye plots and thus greater limits of tolerance of abnormality when comparison is made to normal files. Finally, the polar map tends to exaggerate basal perfusion defects, which are plotted at the bullseye periphery, and tends to minimize defects which are plotted towards the center. Although the volume of myocardium is greater near the base because of the larger ventricular cavity dimension, defect size is nevertheless somewhat distorted, and basal abnormalities may be overestimated. For all of these reasons, in the present study the most apical and most basal portions of the bullseye plot were excluded from the operator-selected lateral and septal regions of interest.

Septal wall motion abnormalities during exercise have been described in patients with LBBB studied with equilibrium radionuclide angiocardiography. In seven patients with rate-related LBBB but no evidence of coronary disease, Bramlet et al. described an abrupt decrease in ejection fraction in six patients, asynchronous left ventricular contraction in all seven, and septal hypokinesis in four patients coinciding with the onset of LBBB during exercise (*11*). Rowe et al. studied 22 patients with LBBB undergoing cardiac catherization, nine of whom were documented to have significant (>50% diameter) coronary stenosis (*2*). Septal wall motion abnormalities occurred in seven of 13 patients without left anterior descending coronary artery stenosis.

Measuring regional myocardial blood flow in dogs with strontium-85 and chromium-51 radioactive microspheres, Hirzel et al. documented that during LBBB induced by right ventricular pacing (mean heart rate = 134 bpm) there was a 26% reduction in blood flow in the septum compared to the lateral wall (*4*). In contrast, in the same dogs during right atrial pacing (mean heart rate = 130 bpm) and normal ventricular depolarization, myocardial blood flow was equal in the lateral and septal walls. Thallium-201 scintigrams performed at the times of microsphere injections also demonstrated a decrease in tracer concentration in the septum only during LBBB induced by right ventricular pacing. These authors speculated that the decrease in septal perfusion may result from compression of septal arteries by the myocardium as a consequence of asynchronous septal contraction. This "squeezing" phenomenon would be more marked at higher heart rates because of shortened diastole and augmented systolic contraction.

In the present study, of the nine patients with LBBB and angiographic normal left anterior descending coronary arteries, five had right coronary artery stenosis. It could be argued that the septal perfusion defects in these patients might be attributable to right coronary artery disease rather than LBBB. In man, 60-100% of blood supply to the septum is provided by septal branches of the left anterior descending coronary artery (*12*). When present, perfusion from the right coronary artery usually supplies only the lower third of the septum (*13*). In a recent study by Brunken et al. ^{201}Tl SPECT was performed in six patients with isolated left anterior coronary disease and seven patients with posterior descending coronary disease (*14*). In patients with posterior descending stenosis the entire septum was abnormal in one case, with the abnormality isolated to the inferior septum in the other six. In contrast, in five of the six cases of left anterior coronary disease, the superior septum and/or the entire septum was abnormal. In our present study, in all patients with right coronary artery disease and LBBB, perfusion abnormalities were noted to involve the entire septum. We therefore conclude that it is very unlikely that right coronary artery disease was a principle cause of septal abnormalities in these patients with LBBB.

In the present study we noted more marked septal perfusion abnormalities in patients who achieved very high peak heart rates (>170 bpm) during exercise. Since at progressively increasing heart rates, the R-R interval decreases but the QRS duration remains relatively constant, ventricular depolarization occupies a progressively greater proportion of the cardiac cycle. Therefore, it is not surprising that septal perfusion and thus septal thallium uptake was less in these patients.

Most exercise-induced septal perfusion abnormalities in patients with LBBB and normal coronary arteries demonstrate redistribution in delayed images. Although the mechanism for such redistribution has not been documented, it may be reasonable to assume that at slower resting heart rates when septal contraction occupies a relatively smaller portion of the R-R interval, ^{201}Tl redistributes, and perfusion defects resolve.

Only one patient we studied with LBBB and stenosis of the left anterior descending coronary artery demonstrated an anterior wall ^{201}Tl perfusion abnormality with normal tracer distribution in the septum. This image pattern may be more specific for left anterior descending coronary stenosis than a perfusion abnormality involving only the septum with or without extension to the contiguous anterior wall. Further investigation of the specificity of such isolated anterior abnormalities in patients with LBBB is warranted.

CONCLUSIONS

In conclusion, our findings indicate that LBBB results in reversible septal ^{201}Tl SPECT perfusion defects. The extent and severity of these abnormalities are indistinguishable in patients with LBBB and left anterior descending coronary stenosis versus those with LBBB and normal coronary arteries. Thus, ^{201}Tl SPECT is indeterminate for left anterior descending coronary artery disease in patients with LBBB.

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