
First-Pass Radionuclide Angiographic Studies of Left Ventricular Function with Technetium-99m-Teboroxime, Technetium-99m-Sestamibi and Technetium-99m-DTPA

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Technetium-99m-teboroxime (BATO) and ^{99m}Tc-sestamibi (MIBI) may provide the opportunity for first-pass evaluation of left and right ventricular function at rest and exercise in conjunction with myocardial perfusion scintigraphy. This study examined the results of age- and gender-matched patients with clinically normal left ventricular function who underwent resting first-pass studies with BATO (n = 25), MIBI (n = 25) and DTPA (n = 25). There were no significant differences between the observed first-pass tracer kinetics or clinical results of MIBI and DTPA. However, there was significantly greater first-pass pulmonary uptake of BATO compared with either MIBI or DTPA. This resulted in five clinically important differences in the BATO FPRNA images: (1) greater background during the levophase of the tracer transit, (2) prolongation of the measured mean pulmonary transit time, (3) lower raw and final ejection fractions, (4) obscured left ventricular border definition resulting in larger geometrically derived left ventricular volumes and (5) poorer image detail and quality which compromised functional image and regional wall motion interpretation. This study suggests that further refinement of the first-pass methodology, particularly with regard to methods of background subtraction, is needed to obtain quality FPRNA results with BATO. However, for the purposes of left ventricular function analysis with FPRNA, MIBI and DTPA are interchangeable.

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First-pass radionuclide angiography (FPRNA) is a noninvasive technique which can detect clinically inapparent ischemic regional and global left ventricular dysfunction with exercise (1). Indices of left ventricular performance derived from FPRNA have important prognostic significance (2), as well as diagnostic value which is both independent from and complementary to myocar-

dial perfusion imaging (3). The assessment of both perfusion and function parameters within a single diagnostic study could optimize the diagnostic evaluation of ischemic heart disease (4-6).

Technetium-99m-labeled perfusion agents, such as ^{99m}Tc-teboroxime (BATO) and ^{99m}Tc-sestamibi (MIBI) provide the possibility of determining both left and right ventricular systolic performance with a bolus injection of the tracer using FPRNA. These tracers will then localize in the myocardium for planar or tomographic perfusion imaging (3,6-11). BATO and MIBI are lipophilic myocardial perfusion tracers (4). FPRNA has usually been performed with water soluble tracers, such as ^{99m}Tc-diethyl-enetriaminepentaacetic acid (DTPA) and [^{99m}Tc]-pertechnetate. Recently, studies have reported that FPRNA with MIBI gives ejection fraction results which are similar to those obtained with gated equilibrium studies (12) and with FPRNA using other tracers (7,13). No such comparisons with BATO have been published to date. Furthermore, the impact of these tracer's first-pass distribution and lipophilicity on the clinical results of FPRNA other than ejection fraction, such as regional wall motion, mean pulmonary transit time and left ventricular volume indices, has not been previously reported. This study examines the characteristics of BATO, MIBI and DTPA for FPRNA indices of left ventricular size and systolic performance in patients with clinically normal left ventricular function.

METHODS

Patient Population

The resting FPRNA studies were performed either for clinical purposes or as an adjunct to an open label trial of BATO at rest and with adenosine perfusion scintigraphy. Informed consent for rest and adenosine teboroxime imaging was obtained from each patient. This investigational protocol was approved by the Institutional Review Board and Radioisotope Research Committees of the University of Chicago. Of 40 patients who participated in this trial, 23 met the criteria of having no prior myocardial infarction by history or ECG, no history of cardiac

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enlargement, heart failure or significant valvular heart disease. Two additional patients were obtained from our clinical files who had undergone BATO FPRNA during diagnostic evaluation and also met these criteria for having clinically normal left ventricular function. This BATO study population consisted of 19 males and 6 females, with a mean age of 54 ± 15 yr.

For comparison, two age- and gender-matched control groups of 25 patients each, who had undergone routine diagnostic FPRNA with DTPA or MIBI, were selected from our clinical files. These data were used to compare first-pass characteristics and tracer dynamics of DTPA, MIBI and BATO.

First-Pass Radionuclide Angiography

Resting FPRNA was performed with a single crystal high-count rate gamma camera fitted with a high-sensitivity, parallel-hole collimator (Elscint Apex 410-M or 409AG, Hackensack, NJ). Anterior projection images were obtained. After measuring resting blood pressure, 25–30 mCi of ^{99m}Tc -BATO, 7–30 mCi of MIBI, or 16–25 mCi of DTPA, each in a volume of less than 1 ml, was given by rapid flushing with 30 ml of normal saline through a large bore indwelling catheter in an antecubital (14- or 16-gauge) or external jugular (18- or 20-gauge) vein. Images were acquired in a 32×32 matrix with a zoom factor of two, in frame mode (typically 20 to 50 msec frames, depending on cardiac cycle length). The total FPRNA acquisition time ranged from 15–40 sec.

FPRNA studies were analyzed using commercially available Elscint computer software (14,15). For computation of ejection fraction, this software creates a left ventricular raw representative cycle by summing frames of several (usually 5–10) cardiac cycles. These cycles are aligned by matching end-diastoles (histogram peaks) and end-systoles (histogram valleys) occurring during the operator defined levophase of tracer transit. The raw ejection fraction is obtained by placing a region of interest (ROI) (guided by a Fourier phase image) over the left ventricle. A background subtracted (final) representative cycle is obtained with the pulmonary frame method (14,15). In this method, a pulmonary background matrix is derived by summing one pulmonary background frame for each cardiac cycle in the raw representative cycle. The initial pulmonary background frame is operator defined at the end-systolic frame prior to tracer entry into the left ventricle. The summed end-diastolic image is then subtracted from the summed pulmonary frame in order to obtain a lung mask image. This mask is then applied to both the background and the end-diastolic frames. The ratio of counts in the background frame to the end-diastolic frame in the masked area (e.g., lung) is then calculated. This determines the fraction of the pulmonary background frame which will be subtracted from the raw representative cycle to create the final background subtracted representative cycle. This fraction is the background subtraction factor. The background corrected representative cycle is then used to determine the final left ventricular ejection fraction (LVEF), as well as the end-diastolic volume using the Sandler and Dodge area-length equation for the anterior projection (16).

The resting LVEF before and after pulmonary background subtraction (i.e., raw and final ejection fractions), the pulmonary background subtraction factor, mean pulmonary transit time, heart rate and geometrically derived end-diastolic volume were tabulated for each test. From these data, left ventricular volume indices, cardiac index and pulmonary blood volume

index (the product of the cardiac index and mean pulmonary transit time) were then calculated. In addition, the final representative cycle was used to create the following functional images: (1) the end-diastolic and end-systolic perimeter image, (2) a regional ejection fraction image, (3) a Fourier phase image and (4) a stroke volume image (end-diastole minus end-systole).

The final image quality was graded for interpretability by one observer on a scale of 1 to 3, where grade 3 = high quality image, grade 2 = irregular image borders, but without compromise of image interpretation, and grade 1 = poor border definition which compromised image interpretation. The 75 sets of images were graded in random order without knowledge of which tracer had been injected.

Data and Statistical Analysis

Unpaired t-testing (comparison of means) was used to determine any differences between the BATO, MIBI and DTPA groups' demographic and FPRNA measurements, FPRNA calculated results and mean image quality grades. These data are presented as mean \pm one standard deviation. In addition, the frequency of each image quality grade was compared for the three tracers using continuity corrected Chi-Square analysis of proportions with one degree of freedom. A p value of less than 0.05 was considered statistically significant.

RESULTS

All patients who underwent BATO injection had marked first-pass uptake of teboroxime in the lungs (Fig. 1). In the presence of this overlying pulmonary tracer activity, subjective visual identification of the left ventricular chamber on the levophase for initial ROI assignment was more difficult with BATO than with DTPA or MIBI. The increased pulmonary extraction resulted in a longer measured mean pulmonary transit time, when compared with DTPA or MIBI (Table 1). The elevated pulmonary background activity resulted in lower raw ejection fractions and higher pulmonary frame background subtraction factors with BATO than were observed with DTPA or MIBI. Also, because of indistinct border definition (Fig. 2), the geometric area-length equation resulted in larger mean cardiac volume indices with BATO when compared with MIBI and DTPA. As a result, the calculated pulmonary blood volume index was significantly higher with BATO than with MIBI and DTPA.

There were no visually evident differences between raw or functional FPRNA images obtained with MIBI and DTPA (Figs. 1 and 2). The measured mean pulmonary transit time with MIBI was essentially identical to that of the DTPA group (Table 1). The raw and final LVEF were similar with MIBI and DTPA, with no significant difference in their ratio. The left ventricular volume indices, calculated cardiac index and pulmonary blood volume index also were similar with MIBI and DTPA.

The quality scores of FPRNA representative cycles and functional images were significantly greater with MIBI and DTPA than with BATO (Table 2). Since image

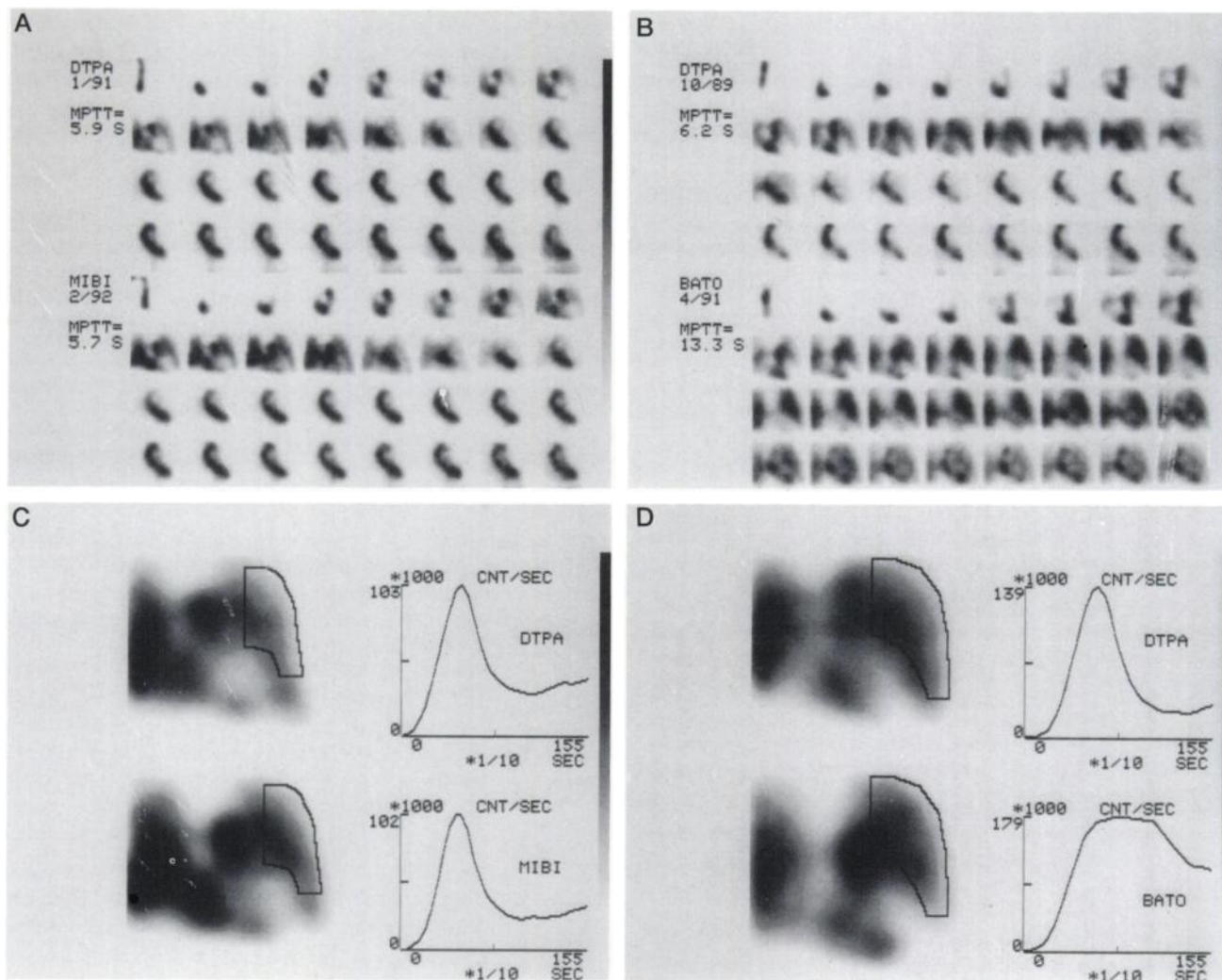


FIGURE 1. Typical FPRNA data of two patients are shown. Serial 0.5-sec (s) summed images (from superior vena cava at upper left, to right heart, lungs, left heart and systemic circulation at lower right) are shown for each of two tracers, a ^{99m}Tc -labeled perfusion agent and ^{99m}Tc -DTPA. (A) Image appearance and mean pulmonary transit time (MPTT) are nearly identical with DTPA (upper four rows) and ^{99m}Tc -sestamibi (MIBI, lower four rows). (B) DTPA (upper four rows) images show a normal transit time and image sequence with the left ventricular phase easily identified. With ^{99m}Tc -teboroxime (BATO, lower four rows), prompt and persistent pulmonary uptake of tracer prolongs the measured MPTT and partially obscures the visual definition of the left ventricular phase. (C) DTPA and MIBI pulmonary frames, left lung ROIs, and resulting time-activity curves for the serial images in A are shown. Rapid pulmonary washout and the onset of the recirculation peak are seen with both tracers within the first 15 sec of the acquisition. (D) DTPA and BATO pulmonary time-activity curves for the serial images of the patient shown in B demonstrate similar tracer inflow but much slower pulmonary washout of BATO relative to DTPA.

quality is directly related to counting statistics, this analysis was somewhat biased against MIBI. For most patients, MIBI FPRNA was performed at rest with a small dose (7 to 10 mCi) as part of a same-day, rest-stress examination. Thus, the average counts in the left ventricular ROI in the raw representative cycle end-diastolic frame were significantly less with MIBI than with our usual doses of 20 mCi of DTPA or 30 mCi of BATO. For BATO, however, the raw end-diastolic left ventricular counts did not clearly relate to better image quality, presumably due to greater contribution of background to counts in the ROI.

DISCUSSION

This study documents the significant impact of a given tracer's first-pass kinetics on the routine clinical FPRNA variables. Although this was not a paired (or triad) comparison of each tracer in the same patients, these findings in subjects with clinically normal left ventricular function agree with those of the multicenter trial (13), documenting that MIBI behaves similarly to conventional tracers, such as [^{99m}Tc]pertechnetate or DTPA for FPRNA LVEF determination. Furthermore, the other important clinical variables derived from FPRNA, i.e., left ventricular vol-

TABLE 1
DTPA,* BATO and MIBI First-Pass Radionuclide Angiographic Results (n = 25 in each group)

Study Parameter	DTPA	p Value	BATO	p Value	MIBI
Raw LVEF	37% ± 4%	<0.001	25% ± 5%	<0.001	36% ± 6%
Background subtraction factor	59% ± 7%	<0.001	71% ± 4%	<0.001	60% ± 6%
Final LVEF	60% ± 7%	<0.02	53% ± 10%	<0.05	59% ± 8%
Final LVEF/raw LVEF	1.6 ± 0.2	<0.001	2.1 ± 0.3	<0.001	1.7 ± 0.2
Pulmonary transit time (sec)	6.5 ± 1.5	<0.001	11.0 ± 3.3	<0.001	6.6 ± 1.6
End-Diastolic volume index (ml/m ²)	90 ± 19	<0.01	106 ± 19	<0.001	84 ± 19
End-Systolic volume index (ml/m ²)	37 ± 11	<0.01	51 ± 18	<0.001	35 ± 13
Stroke volume index (ml/m ²)	53 ± 11	NS	55 ± 8	<0.01	49 ± 8
Cardiac index (L/min/m ²)	4.0 ± 1.0	NS	3.7 ± 1.0	NS	3.6 ± 0.9
Pulmonary blood volume index (ml/m ²)	413 ± 115	<0.001	642 ± 141	<0.001	378 ± 85

*No DTPA—MIBI differences were statistically significant.
NS = not significant.

ume indices, cardiac index, mean pulmonary transit time and pulmonary blood volume index, were found to have the same mean and range of values with MIBI as with DTPA. In this study, there was no observable difference between the initial pulmonary uptake of MIBI and DTPA.

Both MIBI and BATO have excellent myocardial to pulmonary activity ratios at the time of myocardial perfusion imaging (17,18). However, we have observed that BATO has prominent first-pass extraction in the lungs, but with rapid subsequent tracer clearance within the first 2 min after injection. This initial lung uptake results in

important differences in the results of FPRNA, which should be considered when employing this agent. The measurement of mean pulmonary transit time, which is thought to reflect cardiac output, ventricular function, valvular function and pulmonary vascular resistance (19–21) is significantly altered by pulmonary uptake of BATO. Prolongation of the mean pulmonary transit time effects calculation of the pulmonary blood volume index (the product of mean pulmonary transit time and cardiac index). This parameter is routinely measured during FPRNA since a change in pulmonary blood volume index

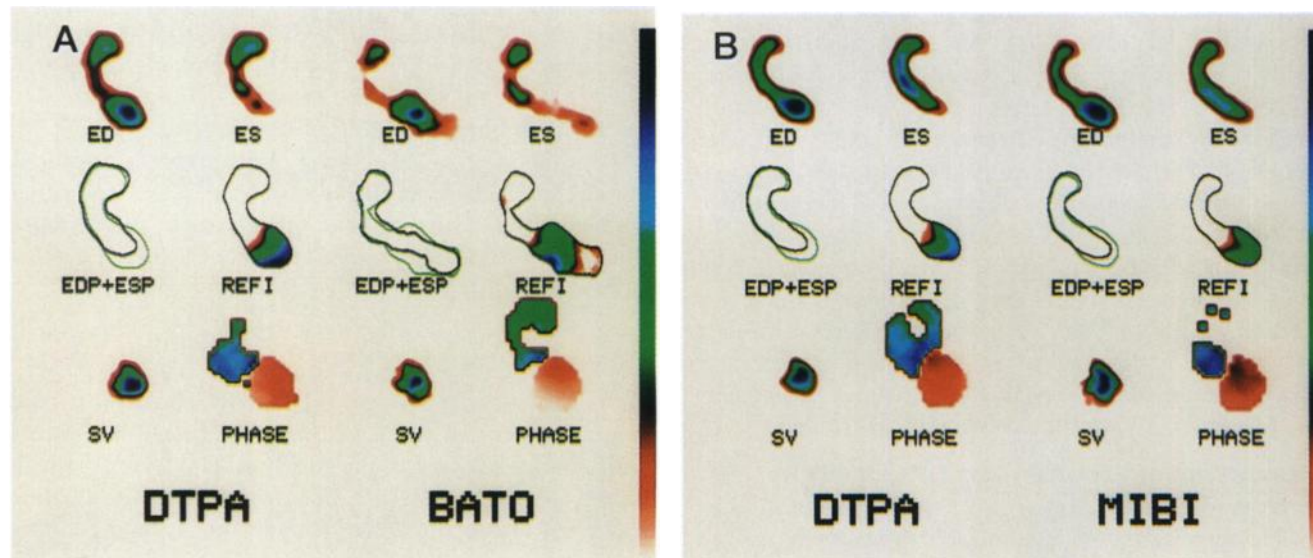


FIGURE 2. FPRNA functional images obtained from the background-subtracted representative cardiac cycle are shown for each of two tracers, a ^{99m}Tc-labeled perfusion agent and ^{99m}Tc-DTPA. ED = end-diastolic image, ES = end-systolic image, EDP + ESP = ED and ES perimeter images, REFI = regional ejection fraction image, SV = stroke volume image and PHASE = Fourier phase image. (A) Image appearance and border definition are essentially identical with DTPA (left two columns) and MIBI (right two columns) in this patient. (B) In another patient, DTPA images show good left ventricular border definition. With BATO, there is unsubtracted periventricular activity (possibly pulmonary activity or first-pass myocardial tracer uptake) which obscures left ventricular border definition. The absence of dynamic activity in this region separates this activity from the left ventricular chamber on SV and PHASE functional images. However, interpretive confusion with an aneurysmal apical segment is conceivable. Of note, the planar BATO myocardial perfusion images (obtained 2 min after FPRNA) were normal at the left ventricular apex in the anterior projection, which confirmed the DTPA findings.

TABLE 2
DTPA, BATO and MIBI First-Pass Radionuclide Angiographic Image Quality Score Comparisons

Image quality scores	DTPA	p Value	BATO	p Value	MIBI
Grade 3 images	20	<0.001	2	<0.001	19
Grade 2 images	5	NS	7	NS	5
Grade 1 images	0	<0.001	16	<0.001	1
Average image grade	2.80 ± 0.40	<0.001	1.44 ± 0.64	<0.001	2.72 ± 0.53
Mean LV end-diastolic counts (raw)	9,661 ± 2,783	<0.1	11,449 ± 3,549	<0.001	7,112 ± 2,547*

*p < 0.01, DTPA versus MIBI; no other DTPA—MIBI differences were statistically significant.
 NS = not significant.

with exercise has been correlated with exercise induced symptoms of dyspnea (22) and an increase in pulmonary capillary wedge pressure (23).

In addition to these important FPRNA variables, the pulmonary uptake of BATO increases the level of background activity during the levophase of tracer transit. This lowers the raw LVEF and increases the percentage of the lung matrix needed for subtraction of pulmonary activity from the background corrected representative cycle. In this study, these factors translated into a significant negative impact on clinical interpretation of FPRNA images. Furthermore, a slightly lower mean FPRNA ejection fraction was found for these clinically normal subjects with BATO than in those imaged with MIBI or DTPA.

Geometric volume assessment requires the determination of the left ventricular area and length (16). Thus, this technique is dependent upon the delineation of the left ventricular borders. In this study, poor edge definition with BATO resulted in larger calculated ventricular volumes while the mean and range of DTPA and MIBI volumes were not significantly different. It could be inferred from this data that determination of left ventricular volume by any method which requires knowledge of the left ventricular borders for ROI definition and the left ventricular counts within that ROI will be adversely affected by the pulmonary background present on first-pass with BATO. These considerations would be important for any of the currently available count-based or geometrically derived left ventricular volume algorithms.

Assessment of Perfusion and Function: Is It Important?

The importance of noninvasive assessment of both myocardial perfusion and ventricular function is underscored by recent studies which demonstrate the impact of such studies on determining prognosis in patients with ischemic heart disease. Prognosis in such patients is closely related to the degree of impairment of resting left ventricular performance (24), exercise ejection fraction (2) and the extent and severity of reversible perfusion abnormalities (25). In patients undergoing cardiac catheterization, noninvasive determination of left ventricular

function can obviate the need for contrast ventriculography along with its hemodynamic (26) and nephrotoxic (27) complications. Thus, the combined assessment of myocardial perfusion and left ventricular function may improve the diagnostic and prognostic value of the non-invasive evaluation of ischemic heart disease.

The results of this study suggest that currently available algorithms for processing FPRNA studies, which were designed for water soluble tracers, may be employed for combined perfusion and function studies with MIBI. However, new methods or standards for analyzing FPRNA studies with BATO are needed in order to obtain ventricular function data with this technique.

Study Limitations

In the absence of injection of each patient with each tracer (paired or triad comparison), it is difficult to establish precisely the impact of BATO tracer kinetics on the measurement of LVEF. However, the finding of a statistically significant difference in unpaired comparisons of BATO with both MIBI and DTPA suggest that this important index of global systolic performance is appreciably altered. This report should serve to stimulate further studies designed to examine direct comparison of these tracers as well as alternative approaches to LVEF measurement with BATO.

CONCLUSIONS

In conclusion, MIBI and DTPA have similar first-pass image kinetics and give similar FPRNA results in subjects with normal left ventricular function. However, the high pulmonary extraction of BATO results in lower ejection fractions, higher pulmonary transit times, higher calculated pulmonary blood volume indices and poorer left ventricular border definition which complicates BATO FPRNA image interpretation.

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