Diagnostic Value of Technetium-99m Radionuclide Angiography for Detecting Thrombosis in Left Atrial Appendage

Toshiisa Uehara, Tsunehiko Nishimura, Kohei Hayashida, and Takahiro Kozuka

Department of Radiology, Cardiovascular Center and Department of Radiology, Osaka University Hospital, Osaka, Japan

In mitral valve disease, it is important to know whether thrombi are present in the left atrium when deciding upon a course of treatment. The left atrial thrombus usually locates in the left atrial appendage. In most cases of mitral valve disease, the left atrial appendage is clearly demonstrated by radionuclide angiography using ^{99m}Tc-labeled red blood cells and it can be speculated that the cases in which left atrial appendage are not demonstrated by RNA have left atrial thrombi. On the basis of this hypothesis, the diagnostic accuracy of radionuclide angiography to detect left atrial thrombi was evaluated retrospectively in 60 patients with mitral valve disease who had undergone surgery. The sensitivity of first-pass and equilibrium radionuclide angiography to detect left atrial thrombi was 83% and 67%, the specificity 79% and 54%, and the accuracy 80% and 57%, respectively. Although there were two false-negative cases in which the left atrial thrombi did not locate in the appendage and 10 false-positive cases in which left atrial appendages were not dilated, the negative predictive value was so high that a clearly demonstrated left atrial appendage can be translated into the absence of left atrial thrombi.

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In mitral valve disease, left atrial (LA) thrombi often cause a critical complication of systemic embolization (*1–4*). A diagnosis of LA thrombus is very important in deciding upon a course of treatment and choosing between percutaneous transluminal mitral commisulotomy (PTMC) or surgical mitral commisulotomy. LA thrombus is formed by stagnation of blood flow and is most frequently seen in the appendage (*5,6*).

The LA thrombus has been diagnosed by echocardiography, cardiac CT scan, contrast pulmonary arteriography, coronary arteriography, or ^{111}In-oxine-labeled platelet scintigraphy. Echocardiography is very useful for observation of the LA cavity but less useful for observation of the LA appendage, and sometimes cannot detect thrombus in the appendage (*7–9*). In mitral valve disease, the left atrium and LA appendage are characteristically enlarged (*10–12*) and are clearly demonstrated by radionuclide angiography (RNA) using ^{99m}Tc-red blood cells. We speculated that nonvisualization of the LA appendage by RNA indicates the presence of LA thrombus and retrospectively analyzed the accuracy of this diagnostic procedure using patients who had undergone surgery. The results were compared with the diagnostic accuracy of transthoracic echocardiography or coronary arteriography.

MATERIALS AND METHODS

Data Collection

First-pass RNA studies were performed by injecting 25 mCi (1.0 ml) of ^{99m}Tc followed by a saline flush (20 ml) in a bolus fashion from medial antecubital vein with an automatic injector (speed of injection; 3–4 ml/sec) 30 min after a venous injection of pyrophosphate. Right anterior oblique (RAO) 15-degree views were imaged by a multi-format camera in 1-sec sequential mode. Non-gated equilibrium images were obtained in the anterior, 30 (40), 45 (50), and 60-degree left anterior oblique (LAO), and left lateral projections. A scintillation camera (Ohio-Nuclear 410 S) with a high-resolution collimator was used.

Image Interpretation

First-pass and equilibrium RNA images were interpreted separately by an experienced observer unaware of the surgical findings, and visualization of the LA appendage was assessed.

In first-pass RNA, the LA appendage was imaged above the left ventricle (LV) and its size was proportional to the LA cavity in the left heart phase. It was easily differentiated from the pulmonary vein, as they appeared in different phases. In equilibrium RNA, the LA appendage was imaged at the same location but differentiation from the pulmonary artery or vein was somewhat difficult. We could not differentiate them on the basis of the phase, so continuity with the left atrium was an important point to differentiate. When the LA appendage was filled with thrombi, it was demonstrated as a photon defect.

Patients

Sixty-five patients who had undergone an open mitral commissurotomy (OMC) or mitral valve replacement (MVR) and preoperative RNA were selected consecutively for this study. Five patients, however, were excluded from this study because their pulmonary circulation was too prolonged to evaluate LA appendage visualization. Therefore, 60 patients with mitral valve dis-

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For reprints contact: Toshiisa Uehara, MD, National Cardiovascular Center, Department of Radiology, 5-7-1 Fujishirodai, Suita, Osaka, 565 Japan.

TABLE 1
Clinical Summary of Patients with LA Thrombus

Patient no.	Age	Sex	LA thrombus surgical findings	Echo findings	Cardiac Cathe	LAA visualization by RNA	
						FP	Equilib
1	59	M	(+) on post wall Orifice of LAA is covered by intima.	(+) on post wall (−) in LAA	(−)	(−)	(−)
2	46	M	(+) on post wall (+) in LAA	(+) just below mitral valve	(−)	(−)	(−)
3	35	F	(+) on post wall (+) in LAA	(+) in LAA	no CAG	(−)	(−)
4	62	F	(+) on post wall (+) in LAA	(+) on post wall (−) in LAA	(+)	(−)	(+)
5	46	M	(+) on post wall (−) in LAA	(+) on post wall (−) in LAA	(+)	(+)	(+)
6	35	F	(+) in LAA (partial)	(−)	(−)	(−)	(−)
7	56	M	(+) in LAA and around orifice of LAA	(+)	(+)	(−)	(−)
8	58	F	(+) huge thrombus (250 g) occupied most of LA	(+) huge thrombus	(−)	(−)	(−)
9	56	M	(+) on post wall (−) in LAA	(+) on post wall (−) in LAA	(+)	(+)	(+)
10	67	F	(+) in LAA	(−)	(−)	(−)	(−)
11	66	M	(+) in LAA	no report	not done	(−)	(−)
12	54	M	(+) on post wall (+) in LAA	(+)	(+)	(−)	(−)

LAA = left atrial appendage.

ease (22 males and 38 females with an average age of 48 ± 11 yr) were examined. In 12 patients, the presence of LA thrombi was confirmed at surgery and 48 patients were free of thrombi (Table 1). Preoperative echocardiography and contrast coronary arteriography were performed in 51 and 49 patients, respectively. Most patients had atrial fibrillation. In our study, non-gated first-pass and equilibrium images were used.

RESULTS

Case Reports

Case 1. A 59-yr-old female patient had mitral stenosis and regurgitation (Fig. 1). Echocardiography did not show LA thrombi. Cardiac catheterization revealed a mitral diastolic mean gradient of 7 mmHg, a mitral valve area of 1.26 cm^2, and regurgitant flow of 2/IV by Sellers' classification (*13*). Coronary arteriography did not show evidence of LA thrombi.

First-pass radionuclide angiograms clearly demonstrated the LA appendage above the LV and to the left of the aortic root in the left heart phase (see the second and third line of Fig. 1A). The anterior view of equilibrium RNA (Fig. 1B) also showed the characteristic image of the LA appendage to the left of the main pulmonary artery. With a LAO 40-degree image, the appendage and the corporal portion of the left atrium were clearly observed,

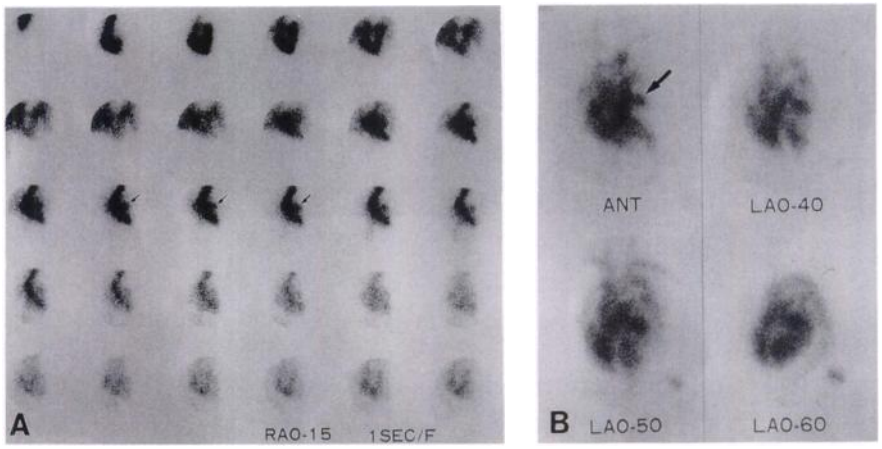


FIGURE 1. (A) First-pass RNA shows a characteristic shape of the LA appendage. (B) Anterior view of equilibrium RNA shows the characteristic shape of a LA appendage.

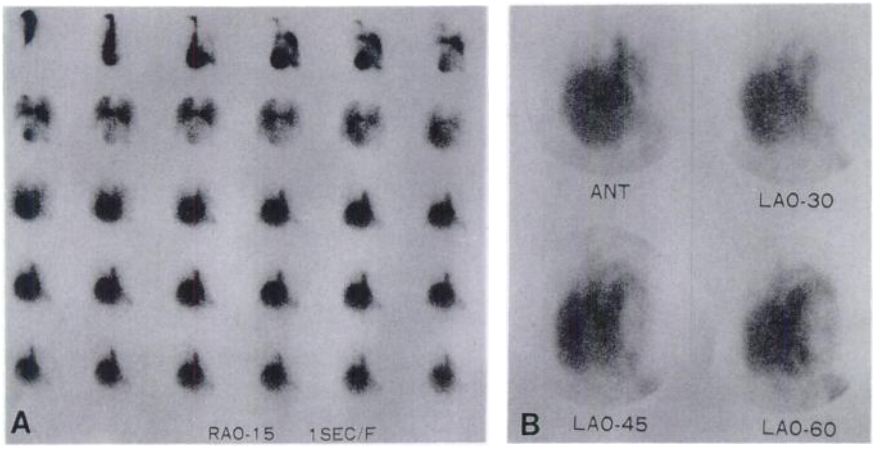


FIGURE 2. (A) First-pass RNA shows a large round LA appendage, but the appendage cannot be seen in the left border. (B) Anterior and LAO views of equilibrium phase RNA do not show the LA appendage.

and therefore, the connecting portion between the appendage and left atrium was also clearly depicted. Open mitral commissurotomy was performed and the absence of LA thrombi was confirmed.

Case 2. A 58-yr-old female had mitral stenosis (Fig. 2). Echocardiography showed marked dilation of the left atrium, marked sclerosis of mitral valve leaflets, and a large mass of thrombi in the left atrium. Computed tomography of the heart also showed a large mass of thrombi in the appendage and posterior wall of the left atrium. Cardiac catheterization disclosed that the mitral diastolic mean gradient was 11 mmHg, the mitral valve area was 0.88 cm^2, and there was no mitral regurgitation.

First-pass RNA demonstrated dilation of the right atrium and pulmonary arteries and marked dilation of the left atrium. Radioisotope was retained in the left atrium, but its left rim was smooth and there was no evidence of the appendage (Fig. 2A). Equilibrium RNA clearly showed the LA despite a clockwise rotation of the heart due to enlargement of the atria (Fig. 2B). With the anterior view, the boundary of the left upper portion of the left atrium (the portion which is considered to be the attaching site of the appendage to the left atrium) was smooth and there was no image indicating the appendage. The LAO views showed a photon defect in the portion above the LA and to the left of the aorta (the portion supposed to be the appendage). OMC was performed and a huge thrombotic mass weighing 250 g was found on the posterior wall of the LA, extending to the appendage.

Case 3. A 41-yr-old female had mitral stenosis (Fig. 3). Preoperative echocardiography and coronary arteriography showed no evidence of LA thrombi. OMC and closure of the LA appendage were performed, although no thrombus could be seen at surgery.

Preoperative first-pass RNA showed a small but characteristic shaped image of the LA appendage in the left heart phase (see the fourth line of Fig. 3A), while in the postoperative RNA this LA appendage image was not seen. This confirmed identification of the LA appendage by preoperative RNA. The equilibrium RNA depicted the LA appendage above the LV and to the left of the pulmonary artery in anterior and LAO 30 views preoperatively, but not postoperatively.

Diagnostic Accuracy of RNA for LA Thrombus

Sensitivity, specificity, and accuracy of first-pass RNA for diagnosing LA thrombus were 83%, 79%, and 80% (Table 2A). There were two false-negative cases, where LA appendages were depicted by first-pass RNA in spite of the presence of LA thrombus at surgery. In these cases, thrombi were located on the posterior wall of the LA with little or no thrombi in the appendage. The number of false-positive cases, where LA appendages were not seen by first-pass RNA in spite of the absence of LA thrombi at surgery, was 10. All of their appendages were found to be too small to be identified by first-pass RNA.

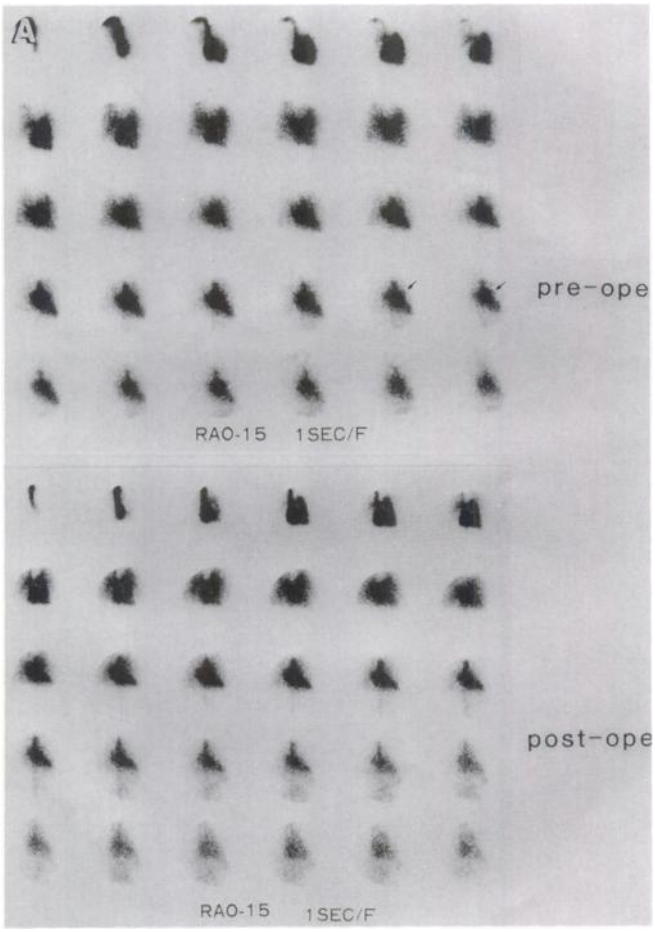
Sensitivity, specificity, and accuracy of equilibrium RNA for detecting LA thrombus were 67%, 54%, and 57% (Table 2B), so all of them were inferior to those of first-pass RNA.

Sensitivity, specificity, and accuracy of transthoracic echocardiography were 82%, 98%, and 94% (Table 3).

Sensitivity, specificity, and accuracy of contrast coronary arteriography for diagnosing LA thrombus by detecting feeding arteries to thrombi or fistula formation to the LA were 56%, 90%, and 84%. Sensitivity was remarkably low (Table 4).

DISCUSSION

The incidence of LA thrombus in mitral valve disease is reported to be 17%–36%, and the incidence of systemic thromboembolism is reported to be approximately 20% (*3,4*). The principal factors contributing to systemic thromboembolism in mitral valve disease appear to be recurrent or chronic atrial fibrillation, a large left atrium and previous embolic episodes (*14*). Indications for surgery, PTMC or antithrombotic therapy is based on the state of the disease process, patients' age, complications and appearance of mitral valve apparatus such as valvular thickening, immobility, subvalvular fusion and calcification (*15–17*). The presence of LA thrombus is one of the important factors in selecting a therapeutic course. Radio-



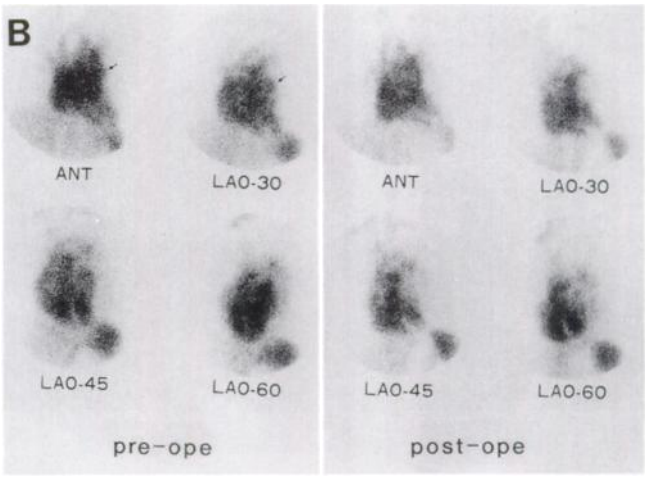


FIGURE 3. (A) Preoperative first-pass RNA image shows a small appendage on the left upper border of the left atrium; postoperative image demonstrates disappearance of the LA appendage. (B) Preoperative anterior and LAO views of equilibrium RNA show a LA appendage, part of which is superimposed by the PA trunk. After surgery, the LA appendage disappeared at the operative closure.

nuclide angiography is useful for detecting the presence of LA thrombi in the LA appendage.

Accuracy of Various Modalities for Diagnosing LA Thrombus

In spite of the development of two-dimensional techniques, the LA appendage is still difficult to observe with echocardiography (*7–9,18–24*). Shrestha et al. reported that sensitivity, specificity, and accuracy of echocardiography for diagnosing LA thrombus in 293 patients with mitral valve disease was 59%, 99% and 92% (*7*), respectively. Fifty-two percent of their false-negative cases had thrombi in the appendage. Schweizer et al. and Baker et al. also reported that in most of false-negative cases by echocardiography thrombi were localized in the appendage (*8,9*). According to Herzog et al., a modified short-axial parasternal view improved detection of thrombi in the LA appendage (*23*). Aschenberg et al., however, in a series of 21 consecutive patients with mitral valve stenosis demon-

TABLE 2
Diagnostic Accuracy of LA Thrombus by (A) First-Pass RNA and (B) Equilibrium RNA

A. Visualization of LA appendage	(−)	(+)	Total
Th (+)	10	2	12
Th (−)	10	38	48
Total	20	40	60
Sensitivity:			83%
Specificity:			79%
Accuracy:			80%
Positive predictive value:			50%
Negative predictive value:			95%

B. Visualization of LA appendage	(−)	(+)	Total
Th (+)	8	4	12
Th (−)	22	26	48
Total	30	30	60
Sensitivity:			67%
Specificity:			54%
Accuracy:			57%
Positive predictive value:			27%
Negative predictive value:			87%

TABLE 3
Diagnostic Accuracy of LA Thrombus by Echocardiography

	LA thrombus by echocardiography (+)	(−)	Total
Th (+)	9	2	11
Th (−)	1	39	40
Total	10	41	51

Sensitivity: 82%; specificity: 98%; accuracy: 94%; positive predictive value: 90%; and negative predictive value: 95%.

TABLE 4
Diagnostic Accuracy of LA Thrombus by Coronary Angiography

	LA thrombus by CAG		
	(+)	(−)	Total
Th (+)	5	4	9
Th (−)	4	36	40
Total	9	40	49

Sensititivy: 56%; specificity: 90%; accuracy: 84%; positive predictive value: 56%; and negative predictive value: 90% .

strated that even with a modified short-axial parasternal view the appendage could be observed in only about 20% of patients and that this technique was beneficial only when the LA was remarkably enlarged. They also tried a transesophageal approach and the sensitivity, specificity, and accuracy of this method for diagnosing LA appendage thrombus were reported to be 100% in the same series (*24*). Transesophageal echocardiography can overcome the limitations of the common transthoracic approach, but the transesophageal technique is troublesome and invasive. In our study, the diagnostic accuracy of echocardiography with transthoracic approach was excellent, but this was the result of the fact that almost all positive cases had thrombi on the posterior wall of the LA. In two cases where thrombi were localized in the appendage, they could not be demonstrated by echocardiography (false-negative cases). Furthermore, the positive cases in this study include cases in which thrombi were not detected by the initial echocardiography but rather were confirmed at the second echocardiography after other diagnostic procedures had demonstrated thrombi. If these cases were excluded, the accuracy was not as good.

The invasive nature of coronary arteriography (CAG) is a drawback to its potential as a screening test for LA thrombi. However, it is commonly performed along with cardiac catheterization in patients with mitral valve disease. The diagnostic clue for LA thrombus in CAG is a fistula formation (a smoke sign) and feeding arteries from the left circumflex artery. In our results, sensitivity of CAG for detecting LA thrombus was low. Similar results were obtained in Colman's study (*25*) where sensitivity was 33%, specificity 99%, and accuracy 83%.

The diagnostic accuracy of pulmonary arteriography for detecting LA thrombus has been reported to be poor (*26–28*) and the method is highly invasive. For these reasons we chose not to perform this examination in this study.

Cardiac CT is excellent for detecting LA thrombus even when the thrombi are localized in the appendage, since recent developments have made it possible to obtain clear gated images in a short time (*29,30*). A considerable amount of contrast media (about 70 ml), however, is required for this technique. We perform CT only when LA thrombus is strongly suspected but not detected by echocardiography. Therefore, only a few cases of this series underwent CT examination and the diagnostic accuracy of CT could not be evaluated.

Indium-111-oxine-labeled platelet scintigraphy is valuable as a functional examination of LA thrombus, since it demonstrates active platelets adhering to the LA wall or already formed thrombus. Yamada et al. reported that sensitivity, specificity, and accuracy of this method for diagnosing LA thrombus was 80%, 100%, and 92%, respectively in their study of 12 cases (*31*). The effect, however, of administered anticoagulant drugs may suppress the activity of labeled platelets and may cause false-negative cases (*32,33*). No patients were examined this way in our study.

RNA has been performed to evaluate various indices of cardiac function, lung congestion and the size of cardiac chambers in mitral valve disease. Careful observation as to whether the LA appendage is depicted by RNA can provide an additional benefit of this method, diagnosis of a LA thrombus. First-pass RNA demonstrated excellent diagnostic accuracy in our study. In two false-negative cases by first-pass RNA, thrombi were localized in the LA body and not present in the appendage. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of first-pass RNA for detecting LA thrombus within the appendage were 100%, 80%, 83%, 50%, and 100%, respectively (Table 5A). Therefore, visualization of the LA appendage by first-pass RNA indicates absence of thrombi within the appendage with high accuracy. A LA thrombus localized outside the appendage, however, cannot be detected by RNA. Furthermore, there were 10 false-positive cases by first-pass RNA in our study and the cause of its misdiagnosis was suspected to be due to appendages too small to be identified by RNA. These cases had small LA bodies and comparatively mild mitral valve disease. Therefore, our results can only be expected in a population with a very high prevalence of dilated atria.

TABLE 5
Diagnostic Accuracy of LA Thrombus Located in the Appendage by First-Pass and Equilibrium RNA

A. Visualization of LA appendate				B. Visualization of LA appendage			
	(−)	(+)	Total		(−)	(+)	Total
Th (+) in app	10	0	10	Th (+) in app	8	2	10
Th (−) in app	10	40	50	Th (−) in app	22	28	50
Total	20	40	60		30	30	60
Sensitivity:		100%		Sensitivity:		80%	
Specificity:		80%		Specificity:		56%	
Accuracy:		83%		Accuracy:		60%	
Positive predictive value:		50%		Positive predictive value:		29%	
Negative predictive value:		100%		Negative predictive value:		93%	

app= LA appendage.

The diagnostic accuracy of equilibrium RNA for detecting LA thrombus was inferior to that of first-pass RNA. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for detecting thrombus within the appendage were 80%, 56%, 60%, 27%, and 93%, respectively (Table 5B). The negative predictive value was good enough to suggest that visualization of the appendage by equilibrium RNA also indicates absence of thrombus in the appendage. The cause of the low diagnostic accuracy of equilibrium RNA is suspected to be due to the difficulty in differentiating the LA appendage from the pulmonary artery or vein. Still, we consider equilibrium RNA to be useful as a supplementary diagnostic measure because it sometimes demonstrates the appendage better than first-pass RNA, as shown in Figure 1. Moreover, in 3 of 10 cases (30%) showing false-positive by first-pass RNA, the equilibrium RNA demonstrated visualization of LAA (true-negative). Inversely in 15 of 38 cases (39%) showing true-negative by first-pass RNA, the equilibrium RNA showed nonvisualization of LA appendages (false-positive).

Identification of the LA Appendage by RNA

Enlargement of the LA appendage is a feature of rheumatic mitral valve disease. This disproportionate enlargement cannot be fully explained by hemodynamic change of the whole LA and is suspected to be caused by direct inflammation of rheumatic fever (*10–12*). Although resolution of RNA images is not good in comparison with other modalities, the enlarged appendage of rheumatic mitral valve disease is easily identified even in RNA images.

In the anterior view of plain chest radiography, the LA appendage is located in the third left arch of the cardiac silhouette and can be differentiated from the great vessels and cardiac chambers. Matsuyama et al. reported that the flatness of the third left arch meant the presence of thrombus in the appendage and sensitivity, specificity, and accuracy of plain radiography for detecting LA appendage thrombus were 60%, 91%, and 83%, respectively (*34*). Although this result supports the fact that the appendage can be observed separately in the anterior view, we performed first-pass RNA in the RAO 15-degree position because the LA appendage could be better depicted long-axially and separately in a slightly RAO projection than in an anterior projection. As for equilibrium RNA, the pulmonary artery trunk is superimposed on the appendage in RAO projection, and therefore, anterior projection is considered to be more advantageous.

The important points to note for identifying the LA appendage in first-pass RNA are as follows: (1) notice the characteristic shape of LA appendage; (2) consider the phase of the image; and (3) fully understand the anatomic location of appendage. Item 2 is important in differentiating the LA appendage from the pulmonary artery and vein. The LA appendage appears following LA body opacification and continues to be seen for a while after the LA body disappears. The appendage is depicted above the base of the left ventricle and in some cases there is a small photon defect between the appendage and left ventricle. Another diagnostic clue is the continuity with the LA body. The shape of the appendage is like a button drop ear (Fig. 4A) or an eagle's beak (Fig. 4B). Differential diagnosis with the pulmonary artery or vein can be done easily based on the phase and the shape in most cases, but differentiation from coronary-pulmonary artery fistula is very difficult because the phase and location of their appearance are almost the same.

In patients whose pulmonary circulation time is prolonged because of massive tricuspid regurgitation and large chambers, ^{99m}Tc cannot reach the LA in a bolus fashion and the left heart is not sufficiently imaged in a limited time by first-pass RNA. Five cases were excluded from this study for that reason.

The important points to note for identifying the appendage in equilibrium RNA are: (1) to recognize the characteristic shape of the appendage and (2) to see the continuity with the LA body in both the anterior and LAO views.

However, some methods for improving RNA image quality might be considered. Gated image or phase analysis did not seem to be helpful because most of these patients had atrial fibrillation and these methods were not suitable for first-pass RNA. Equilibrium SPECT images might improve diagnostic accuracy because SPECT could display LA appendage in separation with other structures, but this approach would require considerable time for acquiring data and reconstructing the SPECT images.

First-pass RNA is usually performed with high sensitivity collimation in order to get high count rates and good statistics for ejection fraction calculations. However, we used high-resolution collimation for first-pass RNA with a 25 mCi injection of ^{99m}Tc. This method, while reducing the count rate by a factor of 4 compared to high sensitivity collimation, provides clearer images. In this study, high-resolution collimation was useful in maximizing spatial resolution of the atrial appendage.

Significance of RNA as a Diagnostic Measure for LA Thrombus

This study showed that RNA was advantageous in detecting thrombi within the appendage that were difficult to detect with echocardiography of a transthoracic approach. The diagnostic accuracy of RNA for detecting appendage thrombus was good. Sensitivity and negative predictive value were excellent, although specificity and positive predictive values were slightly low. This suggests that RNA is very useful in detecting the absence of LA thrombi in LA appendages. If RNA does not demonstrate LA appendages, then echocardiography with a transesophageal approach, although troublesome and invasive, is the technique of choice for detecting LA appendage thrombi.

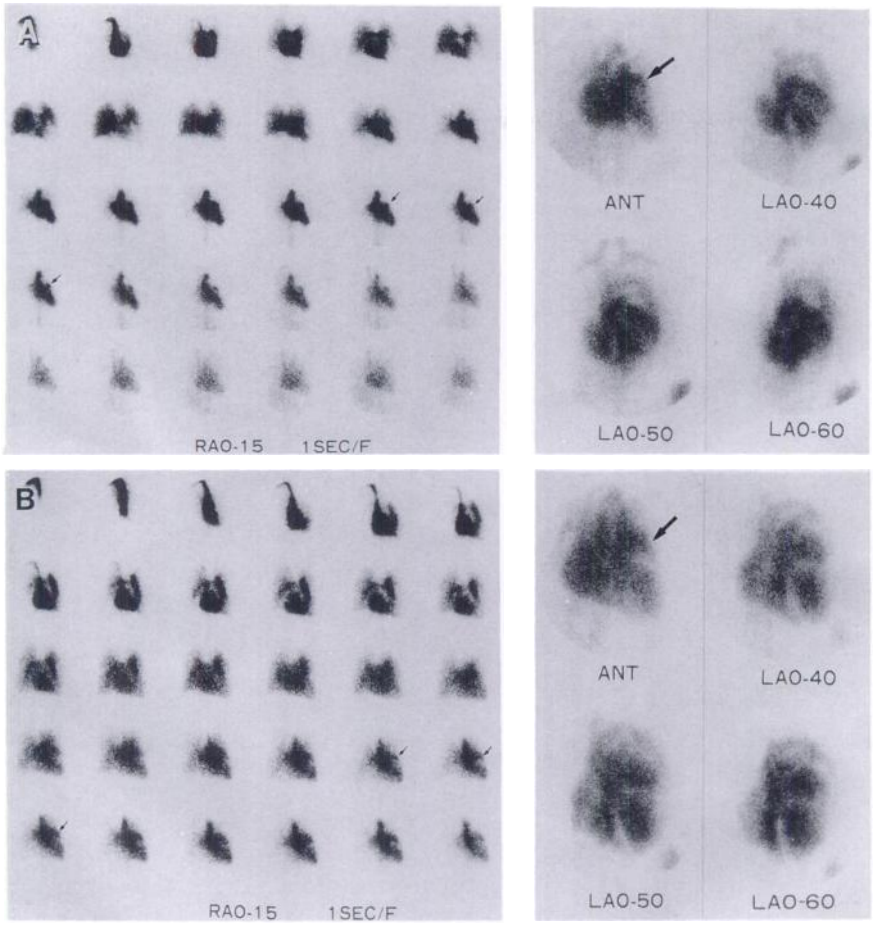


FIGURE 4. Characteristic appearances of LA appendage. (A) Button ear shape. (B) Eagle's beak shape.

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