

# The Significance of Calcific Valvular Heart Disease in Tc-99m Pyrophosphate Myocardial Infarction Scanning: Radiographic, Scintigraphic, and Pathological Correlation

James A. Jengo, Ismael Mena, Stanton H. Joe, and J. Michael Criley

Harbor General Hospital—UCLA, Torrance, California

*Technetium-99m pyrophosphate (PP<sub>i</sub>) is currently considered the best scanning agent for the diagnosis of acute myocardial infarction. False-positive scans have been reported in association with unstable angina, alcoholic cardiomyopathy, and ventricular aneurysms. In this study, 86% of patients (12/14) with either calcific aortic or mitral valvular heart disease had positive PP<sub>i</sub> cardiac scintiscans and the location of the PP<sub>i</sub> uptake was limited to the calcific valve in all (9/9) of the patients who underwent valve replacement surgery. Six patients with valvular disease without radiologic evidence of calcium had negative PP<sub>i</sub> heart images. Three of these patients had surgical valve replacement, and in none was there increased uptake in the resected valve. Seventy-five percent of the patients with calcified aortic valves had localization of the PP<sub>i</sub> activity to the area of the aortic valve, whereas 50% of the patients with calcified mitral valves showed a diffuse pattern of uptake on the cardiac image. In vitro demonstration of increased radioactivity in surgically removed cardiac valves warrants the conclusion that Tc-99m PP<sub>i</sub> is taken up by calcified heart valves. We conclude that while PP<sub>i</sub> heart scanning is a sensitive indicator of acute myocardial infarction, false-positive scans can occur in the presence of calcific valvular disease, due to localization of PP<sub>i</sub> in the calcified portion of the valve.*

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Scintigraphic visualization of an acute myocardial infarction with technetium-99m pyrophosphate (PP<sub>i</sub>) has become a common diagnostic procedure in nuclear medicine. It is a valuable aid in a workup for suspected myocardial infarction.

The mechanism by which Tc-99m PP<sub>i</sub> accumulates in the necrotic myocardial cells has not been fully elucidated. D'Agostino and Chiga (1) observed that after myocardial infarction in humans there is deposition of calcium in the mitochondria of the acutely necrotic cells. The calcium is apparently incorporated into a crystalline structure thought to be hydroxyapatite. Buja et al. (2) have shown the selective occurrence (in the peripheral zones of acute infarction) of calcified muscle cells with ultrastructurally visible apatite-like crystals in the mito-

chondria. They also showed the selective occurrence of high levels of Tc-99m radioactivity in the same tissues. Dewanjee et al. (3), however, found that 50% of the uptake of Tc-99m PP<sub>i</sub> in necrotic myocardial cells was in the lysosomal fraction, and only 10–20% in the mitochondrial fraction. They have postulated that PP<sub>i</sub> is bound to denatured macromolecules.

Using Tc-99m PP<sub>i</sub> scintigraphy, Willerson et al. (4) have shown a 93% accuracy rate in diagnosing acute myocardial infarction. False-positive Tc-99m

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For reprints contact: James A. Jengo, Div. of Nuclear Medicine, Harbor General Hospital, 1000 W. Carson St., Torrance, CA 90509.

TABLE 1. PATIENTS WITH CALCIFIED VALVULAR DISEASE

Patient	Age/sex	Site of valvular disease		Tc-99m PP <sub>i</sub>		Dx
		mitral	aortic	Pattern	Intensity	
1	68 M	—	C	D	+3	CVS
2	52 M	—	C	F	+2	CVS
3	65 M	—	C	F	+2	RHD
4	63 F	—	C	N	0	CVS
5	28 F	—	C	F	+2	CVS
6	47 M	—	C	F	+3	RHD
7	58 M	—	C	F	+3	RHD
8	65 M	C	—	F	+3	RHD
9	55 F	C	—	F	+2	RHD
10	69 F	C	—	D	+3	RHD
11	54 M	C	—	N	+1	RHD
12	50 F	C	—	D	+2	RHD
13	24 F	C	—	D	+2	RHD

Mean: 52

Positive images: 12/14 = 86%

C = calcified valve demonstrated on fluoroscopy or on chest x-ray; F = focal distribution; D = diffuse distribution; N = normal image; RHD = rheumatic heart disease; and CVS = congenital valvular stenosis.

PP<sub>i</sub> cardiac scans occurred in 9% of the patients studied. Seven of the nine patients with false-positive scans had "unstable angina." False-positive Tc-99m PP<sub>i</sub> cardiac scans have also been reported in association with alcoholic cardiomyopathy and ventricular aneurysms (5).

This paper reports on a series of positive Tc-99m PP<sub>i</sub> cardiac scintiscans in patients with calcific aortic or mitral valvular heart disease.

#### METHOD

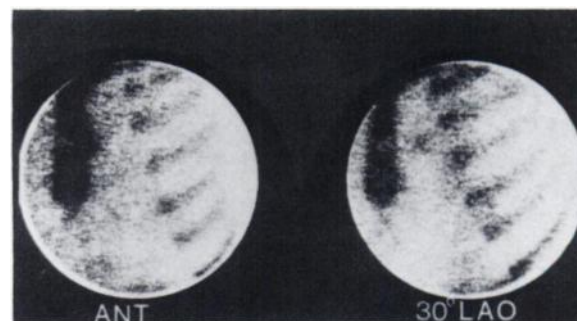
**Patients.** A total of 19 patients was studied, in none of whom was there ECG, or enzymatic (CPK, HBD, SGOT, LDH) evidence of myocardial infarction. They were divided into two groups based on whether there was radiologic evidence of calcified mitral or aortic valves.

1. Patients with calcified valves. Thirteen patients had radiologic evidence of calcification of either the aortic or mitral valve. Eight of these (five aortic and three mitral) subsequently underwent thoracotomy and prosthetic valve replacement.
2. Patients with noncalcified valves. Six patients had either infective endocarditis or rheumatic valvular disease without radiologic evidence of valvular calcification. Three of these patients with infective endocarditis and acute valvular insufficiency underwent surgery with prosthetic valve replacement.

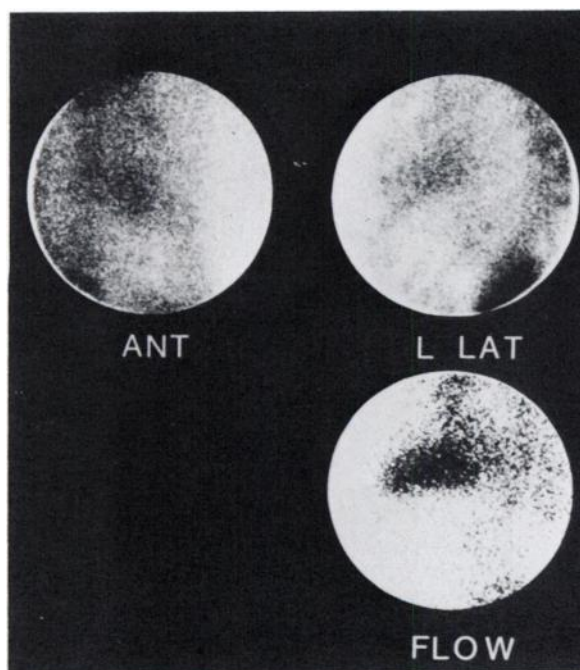
**Radiopharmaceuticals and instrumentation.** All patients were given an intravenous injection of 15 mCi of Tc-99m PP<sub>i</sub> (5 mg). One to two hours after

injection they were imaged in four projections: anterior, 30° and 45° left anterior oblique, and left lateral. The scans were obtained with a scintillation camera using a high-resolution, parallel-hole, 140-keV collimator.

The intensity of the cardiac image was rated from 0 to 4+ using the format of Parkey et al. (6) with 0 and 1+ being within normal limits. The 2+ images are positive but with less intensity than rib uptake; 3+ intensity equals rib uptake; and 4+ intensity exceeds rib uptake. All patients with positive cardiac images were scintiscanned again in the projection that best showed the abnormal activity. Then, without moving the patient, a 10-mCi intravenous bolus injection of [<sup>99m</sup>Tc] sodium pertechnetate was given to obtain a left-heart radionuclide angiogram (LHRA). The location of the abnormal technetium-99m activity could then be correlated



**FIG. 1.** Tc-99m PP<sub>i</sub> cardiac images of Patient 1, in anterior and 30° LAO projections. A +2 focal area of increased activity, best seen in 30° projection, is noted in patient with heavily calcified aortic valve.



**FIG. 2.** Anterior and left lateral Tc-99m PP<sub>i</sub> cardiac images (upper), and corresponding left lateral left heart radionuclide angiogram, of Patient 1. There is a +3 diffuse pattern of cardiac activity.

**TABLE 2. Tc-99m PP<sub>i</sub> UPTAKE WITHIN SURGICAL SPECIMENS: CALCIFIED VALVES**

Patient	Valve	Valve activity (cpm/g)	Skeletal muscle activity (cpm/g)	Ratio: valve/muscle
1	A	39,156	6,022	6.5
4	A	93,372	57,535	1.6
5	A	338,182	140,987	2.4
6	A	343,097	178,082	1.9
7	A	269,275	113,170	2.4
11	M	57,556	27,929	2.1
12	M	1,228,982	298,214	4.1
13	M	253,651	107,420	2.4

Mean  $\pm$  SEM: 2.9  $\pm$  0.6

A = aortic valve; M = mitral valve.

with the left-heart chambers and the ascending aorta.

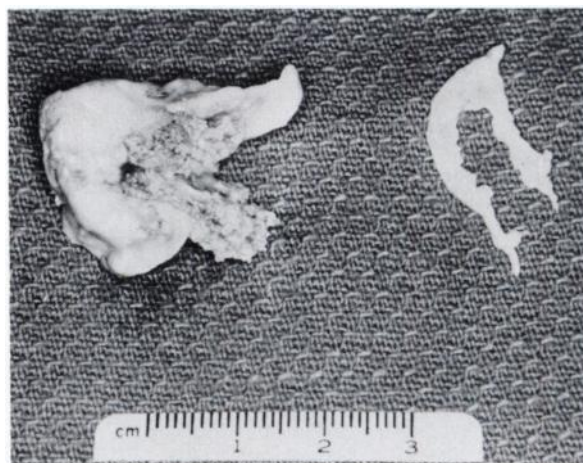
Patients were imaged in each projection until a total of 300,000 counts were obtained (approximately 2 min). The raw data from both the cardiac image and the corresponding LHRA were then fed into a 32K core computer system to produce color displays, each image having either a 64  $\times$  64 or a 128  $\times$  128 matrix. The Tc PP<sub>i</sub> images were displayed in red and the corresponding LHRA in green. Superimposition of the red and green images produced a

third image in which any superimposition of activity generated a new color, yellow.

One and one-half to two hours before the time of valve resection, each patient was given an intravenous injection of 15 mCi of Tc-99m PP<sub>i</sub> (5 mg). The gross surgical specimens were obtained and immediately weighed, counted in a well counter and photographed. The activity of the calcific valves was expressed in counts/minute per gram of tissue. The ratio of activity in the calcified portion of the valve to that of concurrently removed skeletal muscle was then calculated.

## RESULTS

**Patients with calcified valves. Presurgical studies.** Thirteen patients (seven male and six female) with calcific valvular heart disease were studied (Table 1). The ages ranged from 24 to 69 years with a mean of 52 years. Seven patients had shown radiographically calcified aortic valves; the remaining six mitral. Of these 13 patients, 11 (85%) had positive Tc PP<sub>i</sub> cardiac images before surgery. Of the seven patients with calcified aortic valves, five (71%) had focal uptake of PP<sub>i</sub> localizing to the region of the aortic valve as shown by overlay of the LHRA and



**FIG. 3.** (A) Excised aortic valve of Patient 1: heavily calcified, fused right and left cusps on left, and noncalcified noncoronary cusp on right. (B) Scintiscan of excised valve shown in (A): radioactivity was present only in calcified cusps.

TABLE 3. PATIENTS WITH NONCALCIFIED VALVULAR DISEASE

Patient	Site of valvular disease				Tc-99m PP <sub>i</sub> image		Diagnosis
	Age/sex	mitral			Pattern	Intensity	
14	48 M	—	+		N	+1	RHD
15	21 M	—	+		N	0	RHD
16	21 F	+	+		N	+1	IE
17	29 M	+	—		N	+1	IE
18	16 M	+	—		N	0	RHD
19	22 F	+	—		N	0	RHD
Mean: 26					Positive images: 0/6		

N = normal scintiscans; RHD = rheumatic heart disease; and IE = infective endocarditis.

PP<sub>i</sub> images (Fig. 1); one (15%) had diffuse uptake and one (15%) had a normal scintiscan. Of the six patients with calcified mitral valves, three (50%) had diffuse uptake of PP<sub>i</sub> as determined by the overlay method (Fig. 2); one (17%) had a normal image, and two (33%) had focal uptake of PP<sub>i</sub> in the mitral area.

**Surgical studies.** Eight of these patients underwent valve replacement surgery (Table 2) and the ratio of PP<sub>i</sub> uptake of the weight-corrected activity of the calcified valve to skeletal muscle was  $2.9 \pm 0.6$  (mean  $\pm$  SEM) (Figs. 3A and 3B).

**Patients with noncalcified valvular disease. Pre-surgical studies.** Six patients in this category were studied (Table 3), four male and two female. The ages ranged from 16 to 48 years with a mean of 26 years. None had radiographic evidence of calcium within the cardiac silhouette. All six had normal PP<sub>i</sub> heart images. Two of the patients had pure aortic involvement, three pure mitral, and one both aortic and mitral.

**Surgical studies.** Half (3/6) underwent valve-replacement surgery (Table 4) and the weight-corrected ratio of activity of PP<sub>i</sub> mean uptake in the noncalcified valve to skeletal muscle was 0.8.

#### DISCUSSION

The recent surge in the search for an ideal radio-pharmaceutical that would selectively accumulate at the site of an acute myocardial infarction has centered on the bone-seeking agents, especially Tc-99m PP<sub>i</sub>. There is interest in other agents, however, including Tc-99m glucoheptonate (7,8) and Tc-99m tetracycline (9). Of the bone-seeking agents, PP<sub>i</sub> has been found by Bonte et al. (10) to yield the best results in myocardial infarction scanning, both in a comparative animal study and in a series of human studies (4,6).

Bicolor superimposition revealed focal uptake of PP<sub>i</sub> activity over the aortic valve in 75% of the

cases with calcified aortic valves, but in only 33% of the mitral-valve cases, with diffuse uptake in 50%. The mitral valve is a larger structure than the aortic, and its leaflets have greater excursion. This may account for the apparent blurring of the images of the calcified mitral apparatus as compared to the focal uptake over the aortic area.

None of the patients with noncalcific valvular heart disease had positive preoperative Tc-99m PP<sub>i</sub> cardiac scintiscans.

Comparison of the ratio of weight-corrected activity from the resected valve to skeletal muscle revealed that all patients with surgically proven calcific valvular heart disease and positive PP<sub>i</sub> cardiac images had a ratio of activity greater than 1.6:1, with a mean of 2.9:1; whereas their noncalcific counterparts ratios of less than 1.1:1, with a mean of 0.8:1. Thus the valvular uptake of Tc-99m PP<sub>i</sub> in those patients with positive cardiac scans is corroborated by the studies on resected valves.

The diffuse pattern of increased cardiac uptake is a vexing question. Although Patient 1, with a calcified aortic valve, had a markedly increased uptake of PP<sub>i</sub> within the resected aortic valve, his cardiac scintiphoto showed a diffuse pattern of radioactivity. Whether the diffuse uptake represents residual blood

TABLE 4. Tc-99m PP<sub>i</sub> UPTAKE WITHIN SURGICAL SPECIMENS: NONCALCIFIED VALVES

Patient	Valve	Valve activity (cpm/g)	Skeletal muscle activity (cpm/g)	Ratio: valve/muscle
14	A	164,670	293,753	0.6
15	A	168,949	150,000	1.1
17	A	40,477	55,040	0.7
				Mean: 0.8

pool, or increased myocardial activity secondary to ischemia, or small islets of necrosis (1), is a matter for further investigation. However, none of the patients had clinical or laboratory evidence of acute myocardial infarction. Some investigators have suggested that cardiac scanning one to two hours after the time of injection may be too early, especially in those patients with poor osseous uptake.

Calcific aortic or mitral valvular disease, therefore, can be a source of false-positive Tc-99m PP<sub>i</sub> myocardial infarction images. Conversely, noncalcific cardiac valvular disease results in normal PP<sub>i</sub> valve images. We do not feel that the positive PP<sub>i</sub> cardiac scintiphoto due to calcified cardiac valves has lessened the usefulness of the agent in diagnosing acute myocardial infarction. It does, however, help to classify the entities comprising the false-positive scans. Any positive PP<sub>i</sub> cardiac scan, however, will have to be interpreted with care to exclude the presence of calcific valvular heart disease.

We conclude that while Tc-99m PP<sub>i</sub> heart imaging is a sensitive indicator of acute myocardial infarction, it is not specific (4,5) and false-positive studies can occur in patients with calcific valvular heart disease.

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