Myocardial Imaging with Thallium-201: Effect of Cardiac Drugs on Myocardial Images and Absolute Tissue Distribution

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Four cardioactive drugs were studied to determine their effect on the thallium-201 myocardial image. Four unanesthetized dogs were imaged weekly for 14 wk following the administration of dipyridamole, digoxin, furosemide, or propranolol. The myocardial-to-background ratio (M/Bk) was used to define the effects of the drugs on the Tl-201 image. Under control conditions, the M/Bk was 1.99 ± 0.15, which is similar to that in humans. Dipyridamole (0.5 mg/kg i.v.) increased M/Bk to 2.65 ± 0.5. Digoxin, propranolol, and furosemide produced no significant changes in M/Bk.

The relationship between (a) M/Bk derived from external imaging and (b) tissue uptake of Tl-201 was then tested in 12 dogs. Tl-201 concentration (% uptake/gm of tissue) in the heart was significantly elevated after dipyridamole administration as compared with control. Left-ventricular Tl-201 concentration increased 60% ($p < 0.01$). Lung and liver Tl-201 concentration were not significantly altered. Propranolol (0.02 mg/kg i.v.) produced a small reduction in left-ventricular Tl-201 concentration (−11%; $p < 0.01$), but no significant changes in the lung, liver, or kidneys. At rest, only i.v. dipyridamole produced a significant change in the M/Bk; this is consistent with the change in Tl-201 uptake seen in the tissue analysis. Propranolol reduced Tl-201 uptake in cardiac tissue by a statistically significant but small amount, also consistent with the M/Bk data.

The effect of dipyridamole on M/Bk and tissue uptake of Tl-201 suggests that regional perfusion abnormalities may be detected by imaging following coronary vasodilator administration as an alternative to exercise stress. The propranolol data suggest that beta-blockers will have little effect on the resting Tl-201 image.

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Thallium-201 has become the agent of choice for noninvasive myocardial imaging at rest and following exercise. Studies from several centers (*1,2*) and from this laboratory (*3*) have reported the patterns seen with a normal myocardium and the abnormalities induced by myocardial infarction and exercise-induced regional myocardial ischemia. Myocardial uptake of Tl-201 is dependent on both blood flow and cellular ion transport (*4,5*). Hence, it is important to assess the effects on the resulting myocardial image of cardiac drugs that alter one or both

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of these factors. The potential changes induced by drugs are particularly pertinent to investigations involving serial studies to assess the results of surgery and/or the natural history of cardiac disease.

This study reports the effects of several commonly used cardiac drugs (propranolol, furosemide, digoxin, and dipyridamole) on Tl-201 myocardial images, and provides quantitative information on alterations of tissue distribution induced by treatment with propranolol and dipyridamole.

METHODS

Studies were performed on 16 mongrel dogs weighing 18–26 kg and maintained on a standard kennel diet. Serial determinations of BUN and electrolytes were performed weekly in four animals to ensure the adequacy of this diet. For each study, 1–2 mCi of Tl-201, as thallium (I) chloride in sterile saline, were injected through a scalp vein while the awake animal was resting quietly. Thirty minutes later, imaging was performed in the left lateral position with a scintillation camera. The camera was tuned for field uniformity daily and was equipped with a high-resolution parallel-hole collimator. A single FWHM energy window was centered over the 80-keV Hg x-ray peak. Data were collected on Polaroid scintiphotos and stored in a computer system in a 128 × 128 matrix.

In the initial four animals, serial Tl-201 imaging was performed at weekly intervals for 14 wk. Control imaging and imaging following drug treatment were varied in the sequence shown in Fig. 1. Propranolol treatment consisted of 0.2 mg/Kg given intravenously over 1 min, 5 min before Tl-201 injection. Digoxin pretreatment was given as 1.25 mg i.v. 3 hr before imaging. Furosemide was administered as 20 mg orally twice daily for 6 days before imaging. Dipyridamole was administered intravenously (0.5 mg/Kg) 5 min before injection of Tl-201.

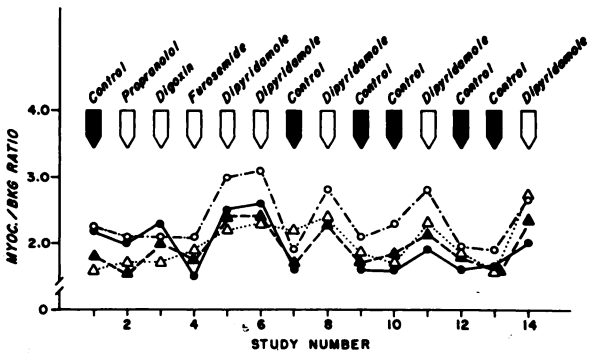

FIG. 1. Myocardium-to-background ratios determined from Tl-201 imaging. Study number indicates separate imaging studies performed at 1-wk intervals. Experimental condition is indicated by arrows in upper portion of panel. The four animals are represented by open and closed circles and triangles. Data from the same animal are connected.

Twelve additional animals were used for both imaging and tissue analysis: four controls, four with propranolol treatment, and four with dipyridamole treatment. Thirty minutes following Tl-201 injection, a blood sample was drawn, the animal killed with a pentobarbital overdose, and imaging performed. Tissue samples were then collected from the anterior, lateral, and posterior walls of the left ventricle and divided into epicardial and endocardial halves. Additional samples were taken from the right ventricle, left atrium, aorta, epicardial fat, liver, lung, renal cortex, renal medulla, and selected skeletal muscles. The samples were weighed and counted in an automatic well counter (50–200 keV window) along with appropriate standards for calculation of percentage of uptake per gram of tissue.

Myocardial-to-background ratios (M/Bk) were determined from the digital scintillation data in the following manner. A ten-channel profile was centered over the myocardium perpendicular to the spine, and the myocardial-to-background profile obtained. Myocardium was taken as the mean of the highest five myocardial points. Background was defined as the mean of the lowest five points overlying the background, these being chosen carefully to exclude edge-packing. We have previously reported excellent reproducibility and small interobserver errors with this method, compared with light-pen methods (*6*). M/Bk was calculated directly as mean myocardial counts per channel divided by mean background counts per channel.

The Student's t test was used for statistical analysis.

RESULTS

Myocardial-to-background ratio. The results of M/Bk measurements in the same four dogs studied serially for 14 wk are shown in Fig. 1. In the 24 control studies, the average M/Bk was 1.82 (s.e.m. = .05; s.d. = .23). The M/Bk obtained following treatment with propranolol, dipyridamole, furosemide, and digoxin are shown in Table 1. Only dipyridamole significantly changed ($p < 0.05$) the M/Bk as measured from the imaging data. However, the four animals pretreated with furosemide did not demonstrate any change in serum potassium (4.2 mEq/l to 4.1 mEq/l), sodium, or BUN; hence it was not possible to assess the degree of potassium depletion, if any. Overall, the measured M/Bk demonstrated considerable variability between individual animals but showed a tendency for any one dog to maintain a persistently high or low M/Bk during consecutive imaging studies under control or treatment conditions. The consistent increase in M/Bk

TABLE 1.

No. of studies	Pretreatment	Myocardial background ratio			
		Mean	s.e.m.	s.d.	Range
24	None (control)	1.82	0.05	0.23	1.57–2.27
19	dipyridamole	2.46	0.07	0.32	1.90–3.10
4	propranolol	1.84			1.55–2.10
4	digoxin	2.03			1.70–2.30
4	furosemide	1.81			1.50–2.10

following dipyridamole is most impressive when each animal is considered individually. Close inspection of Fig. 1 reveals that every animal had an increased M/Bk during each dipyridamole study.

Two representative images from one dog (one control and one following dipyridamole treatment) are shown in Fig. 2. Visually, the myocardial uptake was greater following dipyridamole; and the computed M/Bk increased from 1.9 to 3.1. All images following dipyridamole showed greater myocardial activity compared with control. Images following digoxin and propranolol were not visibly different from control images.

Tissue analysis. The results of tissue analyses are shown in Table 2 and Figs. 3–6. In all animals, the highest concentration of Tl-201 occurred in the kidneys. The control dogs (Fig. 3) had significantly greater Tl-201 activity in renal medulla compared with the cortex. Samples from the left-ventricular endocardium had a greater Tl-201 activity than the corresponding epicardium (0.042 against 0.035% injected dose/gram; $p < 0.001$). Right-ventricular activity was about 75% of left-ventricular activity. Left-atrial activity was only slightly higher than the lung and liver. Samples of skeletal muscle and aorta had roughly 25% of the activity found in the left ventricle. Epicardial fat and blood activity 30 min following the injection of Tl-201 were relatively low.

Changes in tissue Tl-201 distribution following dipyridamole are shown in Table 2. Calculated myocardial activity was significantly increased in all samples ($p < 0.01$). Additionally, the endocardium-to-epicardium (endo/epi) gradient found in the controls was abolished (endo/epi = 1.19 at control and 0.98 post dipyridamole). The percentage change in Tl-201 uptake induced by dipyridamole is shown graphically in Fig. 4. The largest single change was in the right ventricle, which rose from 0.028 to 0.056% injected dose/gram; an increase of 100% ($p < 0.01$). Average left-ventricular activity increased 60% compared with control. Dipyridamole also increased activity in the renal cortex and reversed the medulla-to-cortex gradient noted in the control group. Changes found in the skeletal muscles, aorta, fat, and blood were variable and small. Activi-

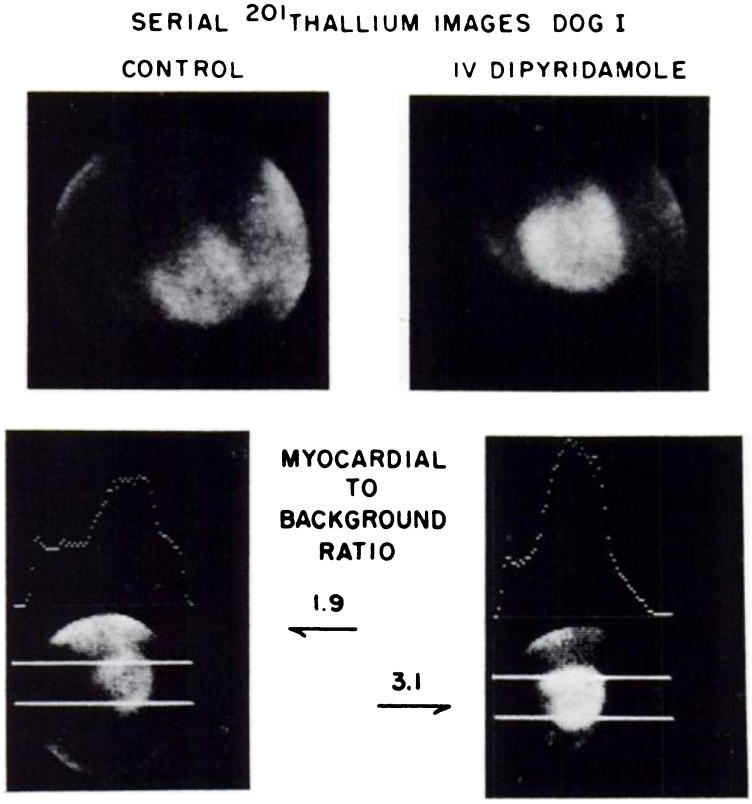

FIG. 2. Serial Tl-201 images in one animal. Control image and profile are at left. Profile images (lower) sum activity between the two white cursors and display the profile curve above. Marked increase in myocardial Tl-201 uptake is seen both visually and by profile analysis in right-hand pair. (Profile images below are rotated 90° from images above.)

TABLE 2.

Sample	Control % inj. dose/g tissue	Dipyridamole % inj. dose/g tissue	Dipyridamole Percentage change	Propranolol % inj. dose/g tissue	Propranolol Percentage change
1 cc blood	.0010	.0010	+3	.0010	−1
Kidney (cortex)	.0477	.0557	+17	.0522	+10
Kidney (medulla)	.0706	.0468	−34†	.0601	−15
Lung	.0159	.0169	+6	.0218	+37
Liver	.0153	.0169	+11	.0128	−17
Skeletal muscle (intercostal)	.0073	.0108	+48	.0073	0
Skeletal muscle (diaphragm)	.0088	.0136	+54	.0094	+7
Skeletal muscle (hind limb)	.0064	.0201	+215	.0067	+5
Skeletal muscle (forelimb)	.0034	.0034	−2	.0045	+32†
Aorta	.0068	.0074	+9	.0083	+22*
Epicardial fat	.0013	.0023	+85†	.0025	+99*
Vent. septum, rt. vent. surface	.0435	.0611	+41†	.0411	−5
Vent. septum, lt. vent. surface	.0351	.0610	+74†	.0337	−4
Avg. V septum	.0393	.0610	+58†	.0374	−5
Ant. LV endocardium	.0424	.0618	+46†	.0380	−10
Ant. LV epicardium	.0345	.0627	+80†	.0267	−23†
Avg. anterior LV	.0384	.0622	+62†	.0324	−16*
Post LV endocardium	.0398	.0596	+50†	.0385	−3
Post. LV epicardium	.0358	.0625	+74†	.0285	−21†
Avg. posterior LV	.0379	.0610	+58†	.0335	−12
Avg. LV endocardium	.0419	.0608	+45†	.0392	−6*
Avg. LV endocardium	.0352	.0621	+77†	.0296	−16†
Avg. L. ventricle	.0385	.0614	+60†	.0344	−11†
Rt. ventricle	.0285	.0559	+96†	.0232	−19†
Lt. atrial appendage	.0178	.0283	+59†	.0109	−39*
LV epicardium/LV endocardium	1.19	0.98		1.32	

* $p < 0.05$.
† $p < 0.01$ compared with control.

ties in the liver and lung were not significantly altered.

In the propranolol-treated animals (Table 2), the changes were less pronounced, but showed significant decreases of Tl-201 concentration per gram of tissue in the left ventricle (−11%; $p < 0.01$), right ventricle (−19%; $p < 0.01$), and left atrium (−39%; $p < 0.05$). The endocardium-to-epicardium gradient was accentuated (1.32 against 1.19 at control). The changes noted in the kidneys, lungs, and liver were

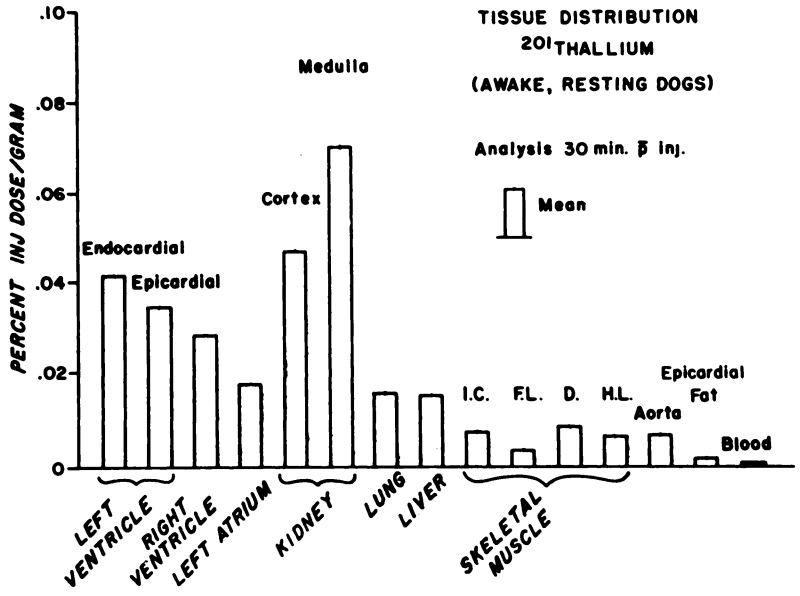

FIG. 3. Data obtained in control animals. Percentage of injected dose of Tl-201 per gram of tissue is indicated on vertical axis ± 1 standard deviation (vertical brackets). I.C. = intercostal; F.L. = forelimb; D. = diaphragm; H.L. = hind limb.

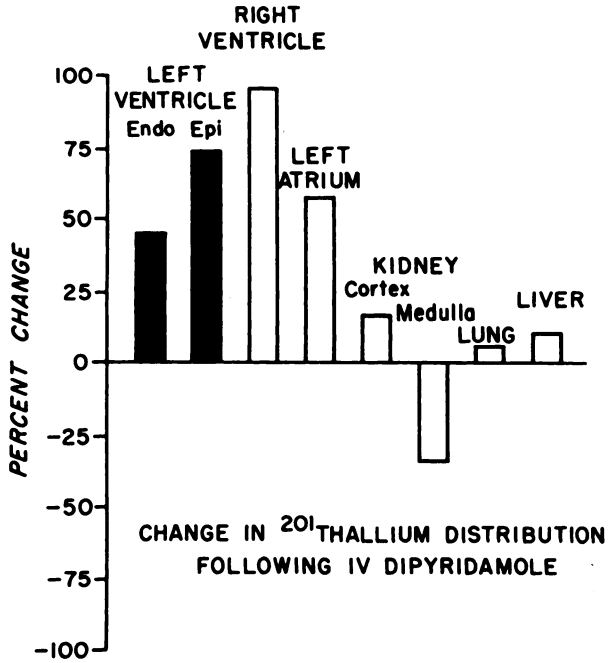

FIG. 4. Change in Tl-201 uptake in selected tissues after administration of dipyridamole. Change in uptake after dipyridamole is expressed as percentage change compared with corresponding control. Organs that make up background in a Tl-201 image (lung and liver) do not show significant changes compared with controls. Myocardial Tl-201 uptake is markedly increased after dipyridamole administration.

not significantly different from control.

Total myocardial uptake. Figure 5 presents the left-ventricular myocardial Tl-201 uptake per gram of tissue under control conditions and after drug interventions. Each point is based on a 6-sample average (3 epicardial and 3 endocardial) for each animal. The average left-ventricular uptake per gram of tissue was .0385% of the injected dose in the control animals, .0344% in the propranolol-treated group, and .0614% in the dipyridamole-treated group. The differences from control are significant ($p < 0.01$) in both treatment groups.

The total right- and left-ventricular uptakes are shown in Fig. 6. For each animal, the percentage uptake per gram has been multiplied by the weight of the right or left ventricle. Left-ventricular uptake was 4.20 ± 0.57% (±1 s.d.) of the injected dose in the control animals, 3.38 ± 0.172% in the propranolol treated group, and 5.56 ± 0.34% following dipyridamole treatment. As above, the propranolol and dipyridamole treatment groups are significantly different from control ($p < 0.05$ and 0.01, respectively). Total right-ventricular uptake of Tl-201 was 1.21 ± 0.21% in the control animals, 0.89 ± 0.21% after propranolol treatment, and 1.82 ± 0.11% after pretreatment with dipyridamole. The dipyridamole mean value is significantly different from control values ($p < 0.01$). The right-ventricular Tl-201 uptake after propranolol pretreatment is not significantly different from control ($p < 0.07$).

Relation between images and tissue distribution. Four typical images from the control and three treatment groups are shown in Fig. 7. Based on simple visual analysis alone, the image following dipyridamole was clearly different from control. The left ventricle is relatively more intense and the right ventricle is easily seen. Myocardial images obtained after digoxin and propranolol treatment were not obviously different from control. The increased M/Bk noted in Table 1 with dipyridamole confirms what is visually obvious. No significant change in mean M/Bk was found in the images obtained following propranolol treatment; thus the minor decrease in myocardial uptake noted in the tissue analysis cannot be appreciated by visual inspection or by analysis of the image.

DISCUSSION

The study demonstrates that commonly used cardiac drugs can alter the tissue distribution and, in particular, the myocardial uptake of Tl-201.

The marked increase in myocardial uptake of Tl-201 following i.v. dipyridamole has not been previously reported, but was not unexpected. Dipyridamole in the dose used is known to increase coronary

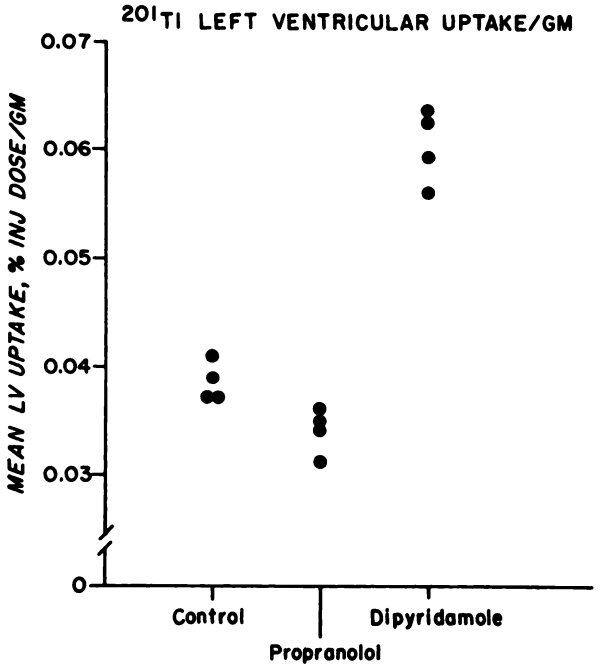

FIG. 5. Left-ventricular Tl-201 uptake expressed as percentage of the injected dose per gram of tissue. Each data point represents average of six tissue samples from left ventricle of one animal. Changes in Tl-201 uptake, compared with control data, are evident after propranolol treatment and are strikingly apparent after dipyridamole treatment.

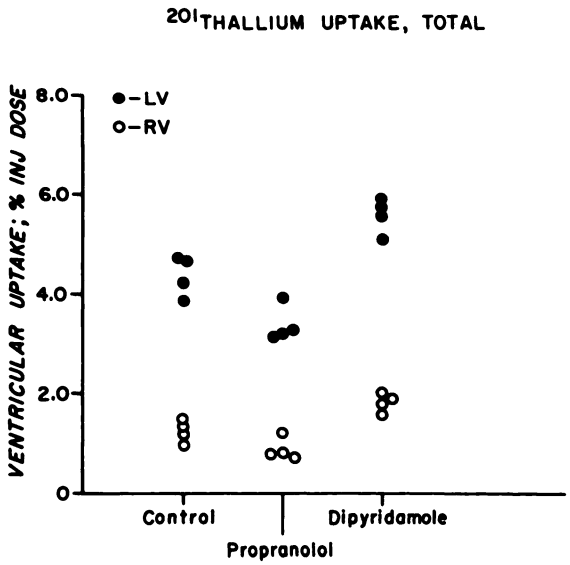

FIG. 6. Total left- and right-ventricular Tl-201 uptake expressed as a percentage of injected dose. Each data point represents the average left-ventricular Tl-201 uptake per gram multiplied by total left-ventricular weight in each animal. Right-ventricular uptake was determined in similar fashion.

blood flow to 3–4 times resting levels (*7*). The 60% increase in Tl-201 myocardial concentration during a period when coronary flow probably increased 3–4 times is of interest, and suggests that thallium uptake is not related to myocardial blood flow in a linear manner. A similar nonlinear relationship between flow and thallium uptake was demonstrated by Strauss et al. (*8*) during periods of reactive hyperemia.

The slight endocardium-to-epicardium Tl-201 gradient noted in the control animals is similar to that noted by Yipintsoi et al. using both microspheres and diffusible tracers (*9*). This presumably reflects higher basal flow rates in the endocardial myocardium. Likewise, the lower concentrations of Tl-201 found in the right ventricle and left atrium are likely due to the lower resting flow rates in these regions of the myocardium. Following dipyridamole, the endocardium-to-epicardium gradient was abolished, suggesting that the normal autoregulatory mechanisms are overcome during dipyridamole vasodilation.

The decrease in Tl-201 myocardial uptake following propranolol treatment is similar to that reported by Costin et al. (*10*). The 11% decrease (per gram of left ventricle) found in our study, however, is less than their figure of 32%. The discrepancy may well be due to their use of anesthetized dogs as opposed to the awake resting dogs used in this study. Diminished Tl-201 uptake following propranolol is probably related to diminished myocardial oxygen consumption and coronary flow induced by beta-blockade (*11,12*). The slight increase in endocardium-to-epicardium gradient following propranolol is also very likely flow-related and has been noted previously with microsphere studies by Becker et al. (*12*).

CLINICAL IMPLICATIONS

The major goal of this study was to ascertain the effects of cardiac drugs on clinical myocardial Tl-201 imaging. The initial serial studies in the same animals suggested that only dipyridamole changed Tl-201 distribution sufficiently to be of clinical significance. The subsequent combined imaging and tissue analysis support this view. Propranolol can alter tissue Tl-201 distribution to a statistically significant degree, but the magnitude of change is small and little or no change is seen in the resultant myocardial images. It should be noted, however, that these studies were performed in resting animals without coronary-artery disease. Hence, our data can be projected only to resting studies in humans; whether they apply to exercise Tl-201-imaging studies is open to question. Propranolol, in particular, may well alter total or regional flow during exercise and does decrease myocardial oxygen consumption (*11*) for a given level of exertion. Either one of these factors could change the regional distribution of Tl-201 in exercising man with coronary disease. Further studies in patients are indicated.

The marked changes in Tl-201 distribution following i.v. dipyridamole suggests a use for coronary vasodilators in imaging studies. First, the increased myocardial uptake greatly improves the Tl-201 images. Second, the induced coronary hyperemia may cause or accentuate abnormalities in regional flow distribution that are not detectable at basal, resting flow rates. The precise mechanism underlying the

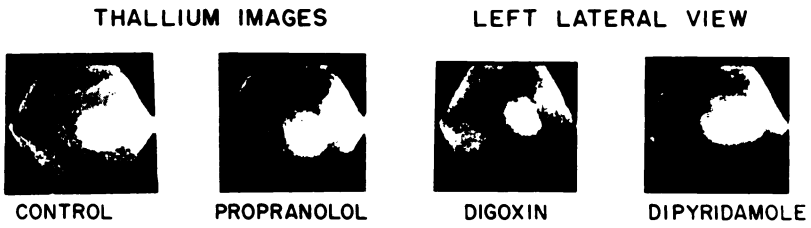

FIG. 7. Left lateral views of heart for control and after drug intervention. Images obtained after propranolol pretreatment and after digoxin pretreatment are not visually different from control. The more intense Tl-201 image after dipyridamole treatment is consistent with increased Tl-201 uptake found by tissue analysis.

exercise-induced Tl-201 defect has not, however, been elucidated and could be related to abnormalities in regional flow, diminished extraction of Tl-201 by ischemic myocardium, or both. If flow maldistribution is the major mechanism, pharmacologic coronary vasodilation could potentially provide an alternative to exercise for the detection of coronary disease.

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