Pharmacologic Stress Testing: Its Roots, Its Impact, and Its Future

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The 1970s was the inaugural decade of stress myocardial perfusion imaging (MPI). Initial imaging with [43]K in 1973 was followed by the potassium analogs [82]Rb in 1974 and ^{201}Tl in 1976. Because of its ease of imaging with the γ-camera, ^{201}Tl became the MPI agent of choice until the clinical availability of the ^{99m}Tc agents in 1990.

Within its first decade, MPI was extensively validated for a wide range of clinical applications including its use for diagnosing coronary artery disease, sizing the magnitude of inducible myocardial ischemia, assessing angiographic stenoses of borderline significance, and evaluating myocardial viability. Initial studies of quantitation were also introduced, providing objective measurements of perfusion defects and, given the washout characteristics of ^{201}Tl, even allowing for the detection of balanced reduction of flow. One particular development in the 1970s was unique and ultimately far-reaching: development of the ability to assess regional myocardial perfusion with pharmacologic agents, thus extending the application of MPI to patients who could not exercise.

In this context, an article in *JNM* published by the late Glenn Hamilton, one of Lance Gould's key collaborators, with Lance Gould as the senior author, has been selected as one of the most important papers in the *JNM* from the 1970s (*1*). This work was one of a series of papers in which Gould and a team of investigators at the University of Washington systematically studied dipyridamole and ^{201}Tl planar imaging in a combination of animal and human studies, after their initial assessments of early coronary blood flow based on contrastinduced coronary vasodilation (*1–3*). Their work with vasodilator stress had a profound effect on MPI. It not only opened the possibility of imaging patients who could not exercise,

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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.

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but also defined the strengths and limitations of imaging with available perfusion tracers, and laid the groundwork for assessing absolute myocardial blood flow and flow reserve. Herein, we highlight their key achievements from that period.

In 1978, they published a series of 6 articles describing MPI with dipyridamole as the vasodilator in dogs and patients. In the initial study using microsphere-measured myocardial blood flow in dogs, they established that the optimal dose of dipyridamole, 0.142 mg/kg/min administered over 4 min, produced an increase in myocardial blood flow 4 min after injection that achieved 95% of maximal flow determined by intracoronary papaverine (2). They further showed that the increase in flow was greater with dipyridamole than with maximal exercise. They simultaneously reported a comparison of ^{201}Tl imaging with both dipyridamole and exercise stress in patients (3), finding improved image quality with dipyridamole stress and that the myocardial-to-background ratio was higher with the patient walking in place after dipyridamole administration—the forerunner of the standard combination of low-level exercise with vasodilator stress that is used today (3). Importantly, in their series of articles, they demonstrated that ^{201}Tl uptake consistently tracked with flow measured by microspheres at flow rates above baseline, but in a nonlinear pattern, confirming an initial observation by Strauss et al. in 1975; that is, as flow increased, the degree of increase in uptake was progressively reduced. In the specific article that was chosen as a highlight for *JNM* in the 1970s, Hamilton and Gould studied ^{201}Tl distribution in normal dogs with several imaging sessions using dipyridamole and other cardiac drugs (1). Their work included tissue sampling during the final session, with correlation to imaging. They observed that dipyridamole increased the tissue concentration of ^{201}Tl by 60%, further supporting the observation of the roll-off of ^{201}Tl uptake at high flow rates.

The pioneering work of this group continues to reverberate throughout cardiac imaging today. Specifically, since its introduction, the use of pharmacologic testing has grown steadily and now constitutes more than half of cardiac stress tests in most clinical laboratories.

Importantly, the mere need to perform pharmacologic testing in lieu of exercise testing has become one of the principal indicators of adverse prognosis, signaling a 2- to 3-fold increase in cardiac and overall mortality risk compared with patients who can exercise at the time of cardiac stress testing (4). The clinical implications of this observation will be investigated for years to come.

Their subsequent work with pharmacologic stress using PET led to the ability to assess absolute myocardial blood flow and myocardial flow reserve (5), which has fueled the marked increase in the use of PET MPI over the last decade. Multiple studies have demonstrated that these measurements add significantly to perfusion defects for prognostic assessment (5) and, more recently, that they can predict survival benefit from coronary revascularization (6). Of note, these measurements solve a central limitation of static imaging with SPECT or PET MPI: that of a balanced reduction of blood flow that does not result in regional perfusion defects, potentially underestimating flow abnormality in patients with extensive coronary artery disease. Interesting, it was through the work of Gould's group in the early 1970s that this phenomenon was first noted. The ability to assess myocardial flow reserve with vasodilator stress has also enhanced the study of coronary microvascular dysfunction, which is the primary cause of ischemia with no obstructive coronary artery disease (7). This syndrome is an increasingly recognized potential source of chest pain and adverse prognosis, particularly in women. Thus, the work of Hamilton and Gould has contributed greatly to the past, present, and future of nuclear cardiology. On a personal note, Glenn was brilliant, was so caring about patients and friends, and had a great sense of humor. Lance is a true and continued inspiring giant in the field.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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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.

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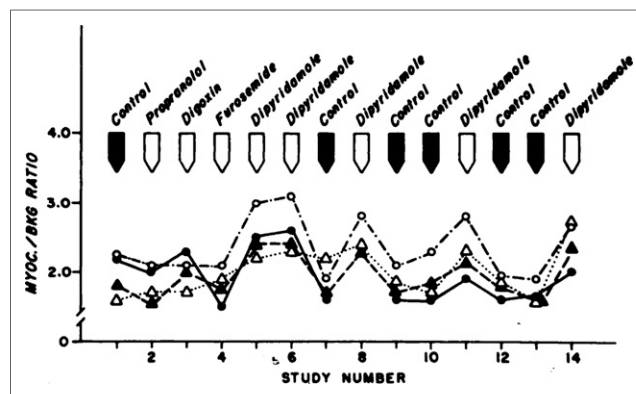
FIGURE 1. Myocardium-to-background ratios determined from Tl-201 imaging. Study number indicates separate imaging studies performed at 1-wk intervals. Experimental condition is indicated by arrows in upper portion of panel. The four animals are represented by open and closed circles and triangles. Data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

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

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/1 to 4.1 mEq/1), 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 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
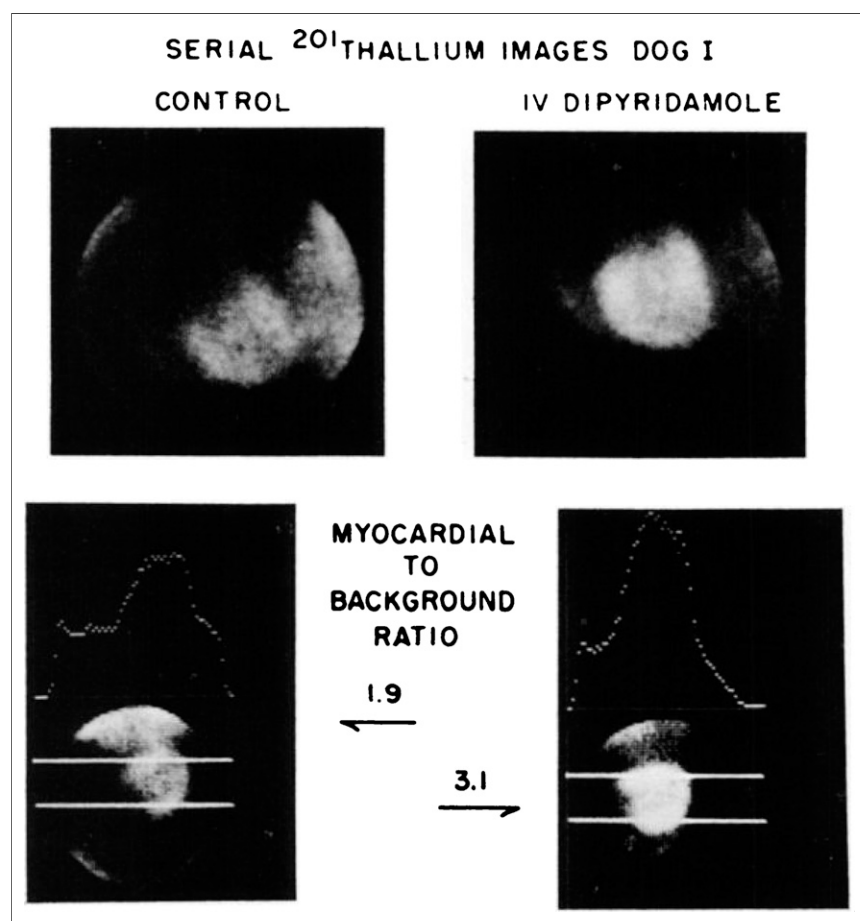
FIGURE 2. Serial Tl-201 images in one animal. Control image and profile are at left. Profile images (lower) sum activity between the two white cursors and display the profile curve above. Marked increase in myocardial Tl-201 uptake is seen both visually and by profile analysis in right-hand pair. (Profile images below are rotated 90° from images above.)

TABLE 2

Sample	Control % inj. dose/g tissue	Dipyridamole % inj. dose/g tissue	Percentage change	Propranolol % inj. dose/g tissue	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.

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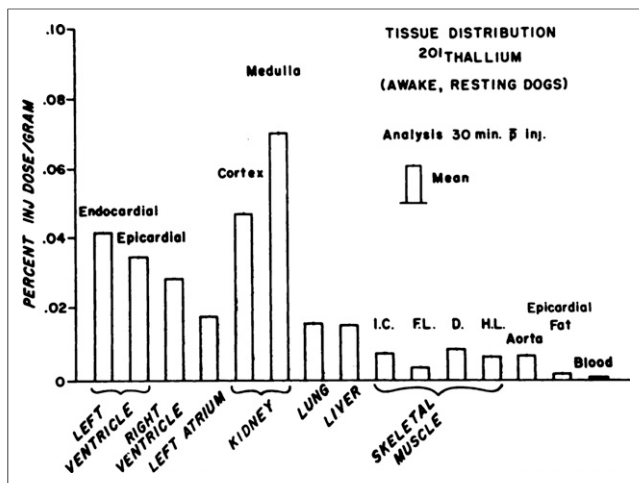
FIGURE 3. Data obtained in control animals. Percentage of injected dose of Tl-201 per gram of tissue is indicated on vertical axis ± 1 standard deviation (vertical brackets). I.C. = intercostal; F.L. = forelimb; D. = diaphragm; H.L. = hind limb.

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 $4.20 \pm 0.57\%$ (± 1 s.d.) of the injected dose in the
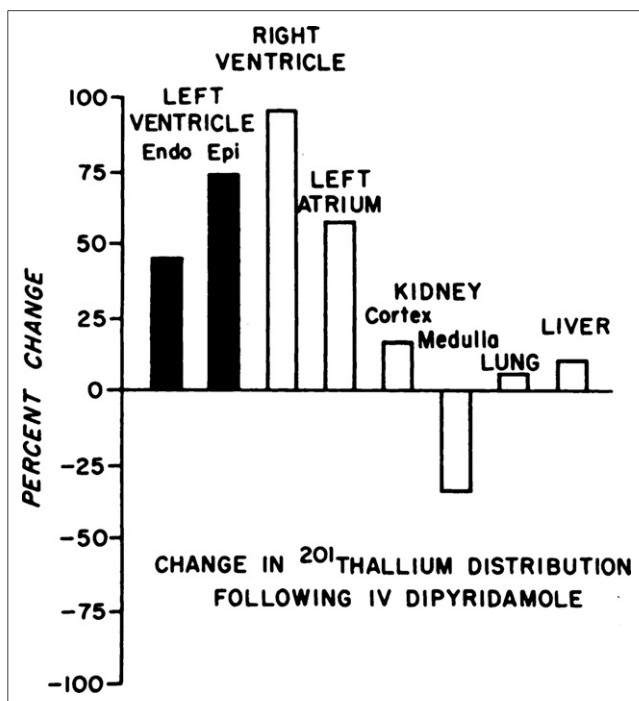

FIGURE 4. Change in Tl-201 uptake in selected tissues after administration of dipyridamole. Change in uptake after dipyridamole is expressed as percentage change compared with corresponding control. Organs that make up background in a Tl-201 image (lung and liver) do not show significant changes compared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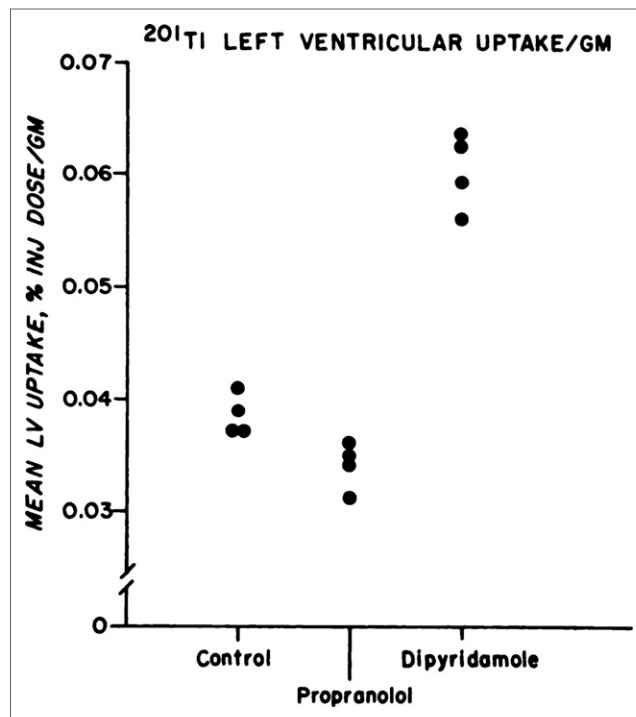

FIGURE 5. Left-ventricular Tl-201 uptake expressed as percentage of the injected dose per gram of tissue. Each data point represents average of six tissue samples from left ventricle of one animal. Changes in Tl-201 uptake, compared with control data, are evident after propranolol treatment and are strikingly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

control animals, $3.38 \pm 0.172\%$ in the propranolol treated group, and $5.56 \pm 0.34\%$ following dipyridamole treatment. As above, the propranolol and dipyridamole treatment groups are significantly
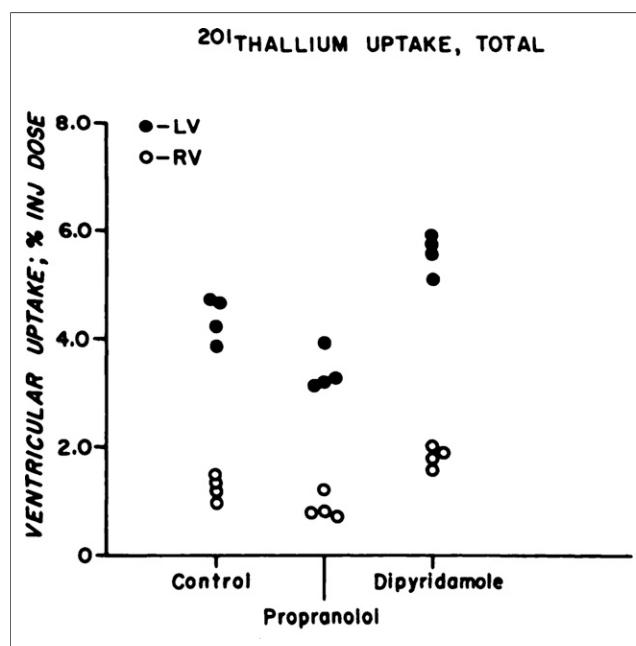

FIGURE 6. Total left- and right-ventricular Tl-201 uptake expressed as a percentage of injected dose. Each data point represents the average left-ventricular Tl-201 uptake per gram multiplied by total left-ventricular weight in each animal. Right-ventricular uptake was determined in similar fashion.

different from control ($p < 0.05$ and 0.01, respectively). Total right-ventricular uptake of Tl-201 was $1.21 \pm 0.21\%$ in the control animals, $0.89 \pm 0.21\%$ after propranolol treatment, and $1.82 \pm 0.11\%$ 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 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 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.

FIGURE 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.

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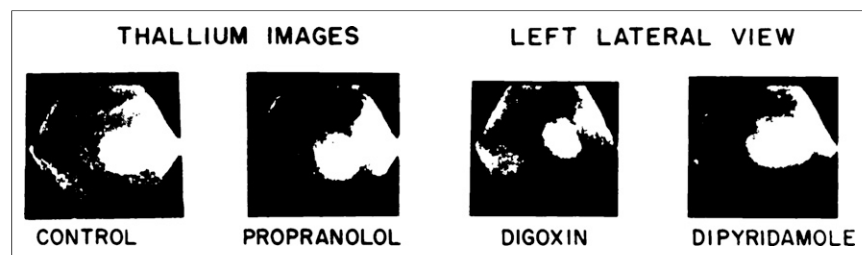
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