Quantification of Walking Exercise Required for Improvement of Dipyridamole Thallium-201 Image Quality

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Dipyridamole ^{201}Tl imaging is an accepted diagnostic procedure for the evaluation of patients unable to perform adequate treadmill exercise, but is limited by high infradiaphragmatic activity. While recent studies have shown that the addition of exercise reduces this activity, the amount of exercise needed to effect such an improvement is uncertain. To prospectively evaluate the amount of walking exercise required to produce improvement in image quality, 120 patients were randomized to either a control group receiving dipyridamole alone, or to dipyridamole supplemented with one of four exercise protocols. Ratios of heart-to-liver and heart-to-adjacent infradiaphragmatic activity were generated from anterior images acquired immediately following the test. Heart-to-total infradiaphragmatic activity was also graded semiquantitatively. Results showed improved target-to-background ratios as well as semiquantitative assessment of image quality for dipyridamole supplemented with exercise as compared to dipyridamole alone. No difference was seen between walking in place and Bruce treadmill exercise at Stage 0 or 0.5. A trend towards higher values was seen with Bruce Stage 1 exercise supplementation, but this did not reach statistical significance. No significant complications occurred during the study. We conclude that 3 min of walking exercise is a safe and effective means of improving the quality of dipyridamole ^{201}Tl images.

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Dipyridamole ^{201}Tl imaging offers a pharmacologic alternative to exercise testing for patients unable to perform an adequate level of treadmill exercise. Dipyridamole is a potent coronary vasodilator and enhances myocardial blood flow in regions supplied by normal coronary arteries, but not in myocardial regions perfused by coronary arteries with significant stenoses (*1,2*). The differential pattern of flow can be imaged with ^{201}Tl (*3–7*). However, nonspecific vasodilatation of the splanchnic bed by dipyridamole results in high infradiaphragmatic background activity that can interfere with interpretation of the images (*8,9*). Recent studies have shown that the addition of low-level treadmill or bicycle exercise improves the quality of these images by increasing the ratio of myocardial to infradiaphragmatic background activity (*10–12*). Since the exercise capacity of patients referred for dipyridamole testing is limited, knowledge of the amount of exercise required to produce an improvement in image quality would be advantageous. Previous reports have not addressed the subject of quantifying walking or treadmill exercise requirements for improved image quality. The present study was undertaken to prospectively evaluate the amount of exercise required to produce improvement in image quality. Four exercise protocols, including walking in place, treadmill exercise at Bruce Stages 0, 0.5 and 1, were compared to a control group receiving dipyridamole alone.

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MATERIALS AND METHODS

Patient Population

One hundred and twenty patients referred to our department for dipyridamole testing over a 10 mo period were entered into the study. This group consisted of 57 female and 63 male patients ranging in age from 28 to 88 yr. Patients were randomly assigned to one of five groups as follows:

Group A: Dipyridamole Alone (Control)
Group B: Dipyridamole + 3 min walking in place
Group C: Dipyridamole + 3 min at Bruce Stage 0
Group D Dipyridamole + 3 min at Bruce Stage 0.5
Group E: Dipyridamole + 3 min at Bruce Stage 1.

It was anticipated that some patients randomized to each of the exercise groups would be unable to perform the assigned exercise, and therefore a larger number of patients was randomized to each of these groups. Twenty patients were randomized to Group A and 25 patients to each of the exercise Groups B–E.

Test Protocols

Patients received 0.56 mg/kg dipyridamole infused intravenously over 4 min. Two and one-half minutes following completion of the infusion, patients assigned to Groups B to E began walking in place or treadmill exercise and continued for 3 min unless limited by angina, hypotension or fatigue. Patients assigned to Group A lay supine for the duration of the test. Thallium-201 (74 MBq) was injected 8 min 30 sec after the start of the dipyridamole infusion in all patients. Figure 1 summarizes the testing protocol.

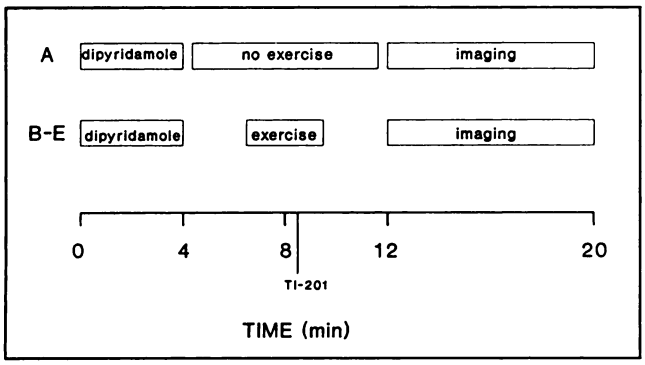

FIGURE 1. Protocols for the five patient groups. A = dipyridamole infusion alone and B–E = dipyridamole infusion supplemented with exercise.

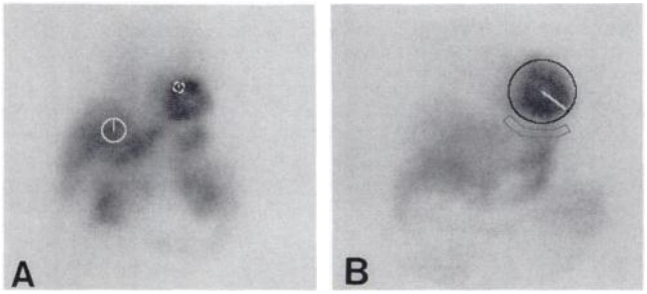

FIGURE 2. Sample ROIs for quantitative analysis of computer images. (A) ROIs placed over peak myocardial and peak liver activity. (B) ROI drawn in an arc below the inferior border of the heart to generate the adjacent infradiaphragmatic activity.

Continuous electrocardiographic (ECG) monitoring, as well as recording of blood pressure and heart rate response were performed on all patients. Horizontal or downsloping ST-segment depression of ≥1 mm at 80 msec after the J point was noted. All side effects of the dipyridamole infusion were recorded, and those that were severe were treated with intravenous aminophylline at the discretion of the supervising physician. Sublingual nitroglycerine was administered when chest pain did not respond to intravenous aminophylline.

Thallium Imaging

Immediately following completion of the test protocol, a single anterior image of the chest and upper abdomen was acquired with a wide field of view integrated gamma camera computer system equipped with a low-energy, general-purpose collimator (Elscint 409, Markham, Canada). Images were obtained in a 256 × 256 byte mode without zoom to a preset time of 480 sec. Routine myocardial images in three standard projections were then collected followed by redistribution images 4 hr later.

Image Analysis

Quantitative and semiquantitative analyses of the initial 256 × 256 computer images were performed as follows.

Quantitative Analysis. A circular region of interest (ROI) was placed over peak myocardial activity, and a second ROI placed over peak liver activity, being careful to avoid overlap from bowel or kidney. These were used to generate the heart-to-liver (H/LIV) ratio. To generate the heart-to-adjacent infradiaphragmatic (H/ADJ) ratio, a circular ROI was placed over the entire myocardium, and a background ROI generated 6 pixels away from the inferior border of the heart. This background ROI was drawn 6 pixels wide in an arc extending from 15° to 105° from the myocardial apex. The ratio of peak heart-to-adjacent activity was calculated. ROI placement is illustrated in Figure 2.

Semiquantitative Analysis. Images were assessed by two independent observers blinded to the test protocols. Heart-to-total infradiaphragmatic activity was graded on a three-point scale as follows: 1 = poor, 2 = average, 3 = excellent. Results from the two observers were averaged for each patient and the mean calculated for each group. Examples of images assessed using this scale are presented in Figure 3.

Statistical Analysis

The significance of differences between means was analyzed using Tukey's test or the Student's t-test. Analysis of discrete quantitative data was accomplished using multiple chi squared tests.

RESULTS

One hundred and twenty patients were randomized to the five protocol groups described above. The age and sex distribution of patients in each of the groups are presented in Table 1. While there were more male than female patients in Groups D and E, chi squared analysis revealed that this was not statistically significant. The proportion of patients able to complete the exercise protocol in each group is illustrated in Figure 4. Three patients in Group E attempted treadmill exercise but were unable to complete the full 3 min protocol. Twenty-six other patients were unable to perform any walking exercise. This included five patients in Group B, four patients in Group C, eight patients in Group D, and nine patients in Group E. These patients were excluded from the analysis.

Heart rate and blood pressure were recorded for each patient. The maximal change in heart rate, systolic and diastolic blood pressures for each group are shown in

FIGURE 3. Examples of semiquantitative analysis. 1 = poor, 2 = good, 3 = excellent.

TABLE 1
Age and Sex Distribution

	Group				
	A	B	C	D	E
Age					
Mean	67	63	60	67	64
Range	54–83	28–79	34–73	36–82	37–88
Sex					
Female	13	14	13	8	9
Male	7	11	12	17	16

A = dipyridamole alone; B = dipyridamole + 3 min walking in place; C = dipyridamole + 3 min Bruce Stage 0; D = dipyridamole + 3 min Bruce Stage 0.5; E = dipyridamole + 3 min Bruce Stage 1.

Figure 5. Peak systolic and diastolic blood pressure were defined in the control group (A) as the lowest blood pressure recorded during the test. In the exercise groups (B–E), peak blood pressure was defined as the maximum systolic or diastolic pressure recorded. No difference was seen in baseline heart rate or blood pressure between the control group and any of the exercise groups. Systolic and diastolic blood pressures in all groups decreased in response to the dipyridamole infusion. In Group A, blood pressure continued to decrease below baseline, whereas in Groups B to E, systolic blood pressure rose significantly ($p < 0.001$) in response to exercise. Diastolic blood followed a similar but more blunted pattern. Heart rate at rest was similar for all groups and rose significantly ($p < 0.001$) in response to dipyridamole in Group A, and in response to dipyridamole and exercise in Groups B to E. The peak changes in heart rate and blood pressure were significantly ($p < 0.05$) higher in the exercise groups than in the control group, but no difference was seen between the exercise groups.

Mean target-to-background ratios and semiquantitative values for each of the protocol groups are presented graphically in Figure 6 and in Table 2. Results follow a similar pattern for all three methods of image analysis. With the exception of the H/ADJ ratio for Group C, all exercise groups yielded mean target-to-background ratios and semiquantitative values that were significantly ($p < 0.05$) higher than those of the control group. In comparing the effect of the different exercise protocols on image quality, we found that walking in place and Bruce treadmill exercise at Stages 0 and 0.5 yielded values that were similar. There was a trend towards higher mean ratios at Bruce Stage 1, but this did not reach statistical significance.

Three patients attempted Bruce Stage 1 treadmill exercise but did not complete the 3 min protocol. Two patients completed 2 min 15 sec of exercise, and the third patient completed 2 min 20 sec of exercise before discontinuing because of fatigue. Their results were excluded from the mean values calculated above. By examining this small subgroup of patients separately, we found the mean H/

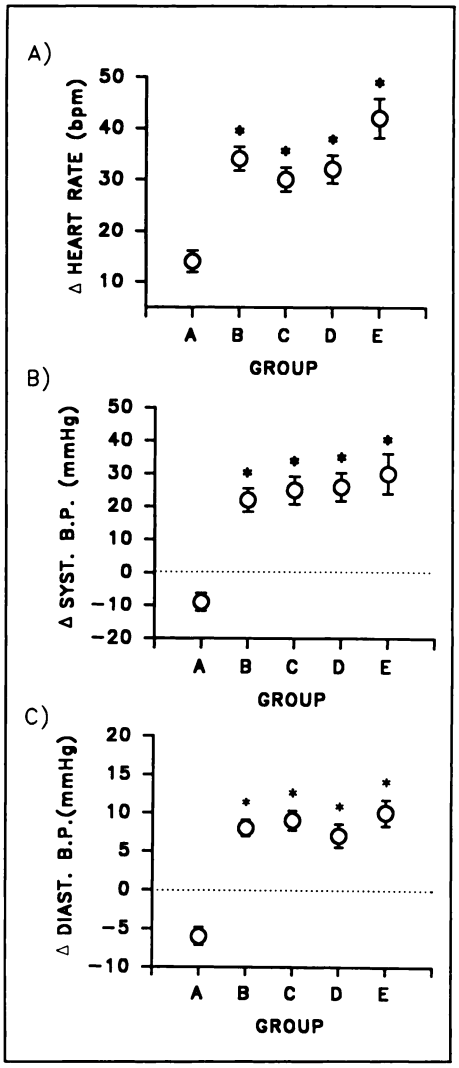

FIGURE 5. Hemodynamic response. The peak change in heart rate (A), systolic (B) and diastolic (C) blood pressure for each of the five protocol groups. * $p < 0.05$ compared with Group A.

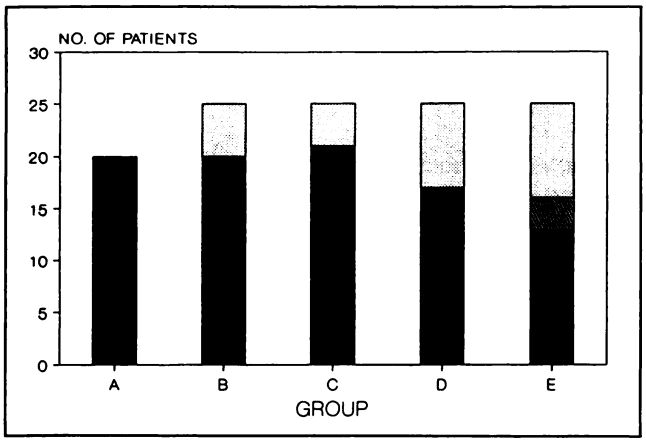

FIGURE 4. Number of patients completing the test protocols. ■ completed 3 min of exercise, ▨ unable to complete the full 3 min of exercise, □ unable to perform any walking exercise.

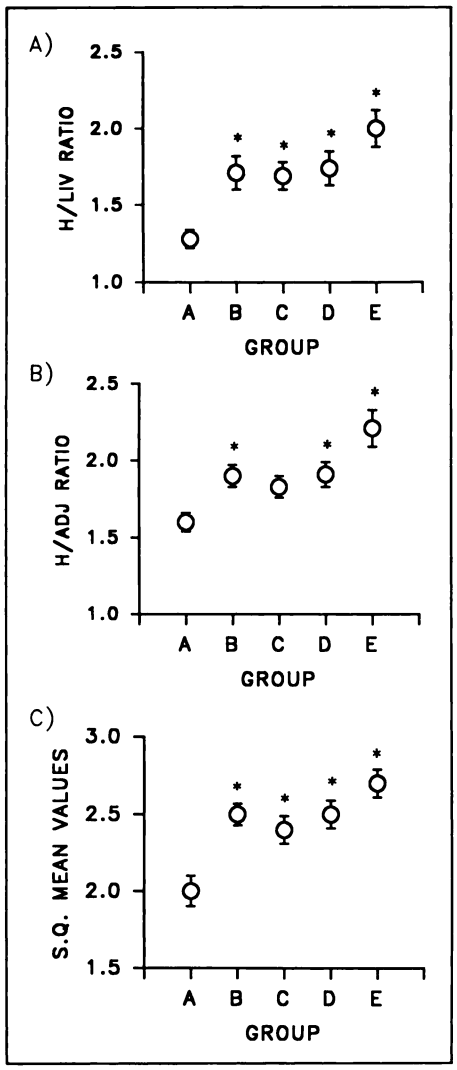

FIGURE 6. Target-to-background ratios and semiquantitative analysis results. (A) Heart-to-liver (H/LIV) mean ratios. (B) Heart-to-adjacent infradiaphragmatic activity (H/ADJ) mean ratios. (C) Semiquantitative (S.Q.) assessment mean values. * $p < 0.05$ compared with Group A.

LIV ratio of 2.13 and the mean H/ADJ ratio of 1.84 to be higher than the mean values for the control. Although a statistical comparison cannot be made because of the small number of patients in this subgroup, it appears that patients who exercise at Bruce Stage 1 but do not complete the protocol still demonstrate improved image quality over dipyridamole alone. It is not clear, however, whether these patients would show the same degree of improvement in image quality as patients who successfully complete the full 3-min Stage 1 protocol.

All side effects experienced during the test protocols were recorded. Whenever possible, differentiation was made between cardiac and noncardiac chest pain, and the results of this and other side effects are presented in Table 3, including the number of patients requiring aminophylline. Chi squared analysis of the data showed no significant difference in the incidence of side effects or in the administration of aminophylline between the groups.

TABLE 2
Qualitative and Quantitative Assessment of Target-to-Background Ratios

Group	H/LIV	H/ADJ	S.Q.
A	1.28 ± 0.06	1.60 ± 0.06	2.0 ± 0.1
B	1.71 ± 0.11*	1.90 ± 0.07*	2.5 ± 0.07*
C	1.69 ± 0.09*	1.83 ± 0.07	2.4 ± 0.09*
D	1.74 ± 0.11*	1.91 ± 0.08*	2.5 ± 0.09*
E	2.00 ± 0.12*	2.21 ± 0.13*	2.7 ± 0.09*

All results are presented as mean ± s.e.
S.Q. = semiquantitative assessment.
* $p < 0.05$ compared with Group A.

ST-segment depression of ≥1 mm during the procedure was recorded. Patients with resting ECG changes which precluded interpretation of the ST-segment were omitted from this analysis. The results are presented in Table 4. The incidence of ST-segment depression in each of the exercise groups was higher than the control group, although the differences were not statistically significant.

DISCUSSION

A significant proportion of patients with suspected coronary artery disease are unable to perform sufficient treadmill exercise to provide diagnostic or prognostic information. Dipyridamole ^{201}Tl imaging offers an alternate method of assessing coronary artery disease in this group of patients (*1–5*). Although significantly limited in their exercise capacity, the majority of these patients are able to perform a modest amount of treadmill exercise, and this has been shown to significantly improve image quality. Gould et al. supplemented dipyridamole with walking in place and demonstrated a higher heart-to-lung ratio than for dipyridamole alone (*2*). They did not examine the effect of exercise supplementation on infradiaphragmatic activity. Casale et al. demonstrated improved heart to liver ratios following supplementation with low-level treadmill exercise (*10*). In a prospective randomized study, we have previously shown significant improvement in heart to

TABLE 3
Incidence of Side Effects

	Group				
	A	B	C	D	E
Angina	3 (15%)	8 (40%)	6 (29%)	4 (24%)	4 (31%)
Noncardiac chest pain	5 (25%)	2 (10%)	2 (10%)	1 (6%)	1 (8%)
Headache	0	0	0	0	0
Dizziness	0	0	0	1 (6%)	0
Nausea/Flushed feeling	0	0	0	0	0
Aminiphylline administered	8 (40%)	11 (55%)	8 (38%)	8 (47%)	7 (54%)

TABLE 4
Incidence of ST-Segment Depression

Group	n	No.	%
A	12	1	8
B	11	2	18
C	14	3	21
D	13	4	31
E	11	3	27

infradiaphragmatic activity for those patients supplemented with treadmill exercise as compared to handgrip exercise or dipyridamole alone (*11*). Hurwitz et al. have shown decreased splanchnic-to-myocardial ratios in patients supplemented with supine bicycle exercise (*12*). In these studies, there was no systematic attempt to quantitate the amount of exercise needed to improve image quality. The purpose of this prospective study was to quantify the amount of walking exercise required to produce a statistically significant improvement in image quality.

We compared dipyridamole supplemented with four standardized levels of walking exercise to a control group receiving dipyridamole alone. The protocol used in this study was designed to exercise patients for a standard length of time, with injection of ^{201}Tl 1 min prior to the end of exercise to permit circulation and uptake of the radiotracer during peak exercise. Our previous study showed that the maximum exercise capacity of the majority of these patients was 3 min at Bruce Stage 1. Therefore, we chose this as our maximum level of exercise, comparing it to two lower levels of the Bruce treadmill protocol (Bruce Stages 0.5 and 0) and to walking in place. Walking in place was included since, if effective, it would afford a means of improving dipyridamole image quality in patients unable to perform any treadmill exercise, as well as in nuclear medicine departments without access to treadmill equipment.

The majority of patients assigned to exercise (71%) were able to complete the protocol to which they were assigned. Twenty-six patients were unable to perform any walking exercise at all. All patients who attempted treadmill exercise at Bruce Stages 0, 0.5, or walking in place were able to complete the full 3 min of the exercise protocol. Three patients assigned to Bruce Stage 1 attempted exercise but were unable to complete the full 3 min protocol. Fewer patients attempted exercise at the higher stages of the Bruce protocol (Groups D and E). Since patients were randomized prospectively to the exercise protocols, it is unlikely that this represents a true difference in the exercise capacities of the patients in these categories. Rather, we noticed a reluctance on the part of some patients assigned to the higher stages of the Bruce protocol to even attempt treadmill exercise.

Walking exercise demonstrated significantly improved target-to-background ratios as well as semiquantitative assessment of image quality over dipyridamole alone. This was seen in all categories with the exception of the H/ADJ ratio of Group C. No difference was demonstrated between walking in place, treadmill exercise at Bruce Stage 0 or stage 0.5. Presumably the workload performed during these protocols results in a similar reduction in splanchnic flow and/or an increase in coronary flow so that the ultimate target-to-background ratios are essentially the same. A further improvement in image quality may be achieved at the higher stage of the Bruce protocol, although when compared with walking in place, this did not reach statistical significance.

Prior to performing the dipyridamole test, the exercise tolerance of an individual patient can only be estimated. Although there does not appear to be any advantage in exercising patients at Bruce Stage 0 or 0.5 as compared to walking in place, there may be an additional improvement in image quality if patients are exercised for 3 min at Bruce Stage 1. Corollary information such as assessment of exercise capacity, exercise induced chest pain and ST-segment displacement may also be obtained. However, a certain number of patients allocated to this level will not complete the protocol. If the few patients in this category are an accurate reflection of this subgroup, it would appear that these patients would still show an improvement in image quality over dipyridamole alone.

The improvement in image quality seen with exercise did not result in an increased incidence of side effects. In this, and previous studies, several hundred patients have undergone exercise supplementation of dipyridamole testing without significant complications (*10–14*).

Reports in the literature, including the results of our previous study, have found the incidence of ST-segment depression to be higher in groups exercised following dipyridamole infusion when compared with dipyridamole alone (*10–13*). In this study, ST depression showed a higher trend in the exercise groups compared with the control, although this did not reach statistical significance. This may be a reflection of the small numbers of patients in the groups, as well as the low level of exercise performed by the majority of patients in our study.

We conclude that 3 min of walking exercise significantly improves the quality of dipyridamole ^{201}Tl and is safe. Although patients referred for dipyridamole testing are limited in their exercise capacity, our experience shows that the majority of patients are able to perform sufficient walking exercise to significantly improve image quality. Walking in place was as effective as treadmill exercise at Bruce Stages 0 and 0.5. This offers a simple method of improving dipyridamole image quality for patients unable or unwilling to perform treadmill exercise. A trend towards further improvement in image quality over walking in place is seen with the higher level of exercise (Bruce Stage 1).

REFERENCES

1. Gould KL, Westcott RJ, Albro PC, Hamilton GW. Noninvasive assessment of coronary stenoses by myocardial imaging during pharmacologic coro-

nary vasodilation II. Clinical methodology and feasability. *Am J Cardiol* 1978;41:279–287.
2. Albro PC, Gould KL, Westcott RJ. Noninvasive assessment of coronary artery stenoses with myocardial perfusion imaging during pharmacological coronary vasodilation III. Clinical trial. *Am J Cardiol* 1978;4:751–760.
3. Leppo J, Boucher CA, Okada RD, Newell JB, Strauss HW, Pohost GM. Serial thallium-201 myocardial imaging after dipyridamole infusion: diagnostic utility in detecting coronary stenoses and relationship to regional wall motion. *Circulation* 1982;66:649–657.
4. Gould JL. Pharmacologic intervention as an alternative to exercise stress. *Semin Nucl Med* 1987;17:121–130.
5. Leppo JA. Dipyridamole thallium-201 imaging: the lazy man's stress test. *J Nucl Med* 1989;30:281–287.
6. Beller GA, Holzgrefe BS, Watson DD. Effects of dipyridamole-induced vasodilation on myocardial uptake and clearance kinetics of thallium-201. *Circulation* 1982;68:1328–1338.
7. Josephson MA, Brown BG, Hecht HS, Hopkin J, Pierce CD, Peterson RB. Noninvasive detection and localization of coronary stenosis in patients: comparison of resting dipyridamole and exercise thallium-201 myocardial perfusion imaging. *Am Heart J* 1982;103:1008–1018.
8. Brown BG, Josephson MA, Peterson RB, et al. Intravenous dipyridamole combined with isometric handgrip for near maximal acute increase in coronary flow in patients with coronary artery disease. *Am J Cardiol* 1981;48:1077–1085.
9. Laarman GJ, Bruschke AVG, Verzijlbergen JF, et al. Efficacy of intravenous dipyridamole with exercise in thallium-201 myocardial perfusion scintigraphy. *Eur Heart J* 1988;9:1206–1214.
10. Casale PN, Guiney TE, Strauss HW, Boucher CA. Simultaneous low level treadmill exercise and intravenous dipyridamole stress thallium imaging. *Am J Cardiol* 1988;62:799–802.
11. Stern S, Greenberg ID, Corne RA. Effect of exercise supplementation on dipyridamole thallium-201 image quality. *J Nucl Med* 1991;32:1559–1564.
12. Hurwitz GA, Powe JE, Driedger AA, et al. Symptom-limited exercise for myocardial perfusion scintigraphy: image characteristics and clinical role. *Eur J Nucl Med* 1991;17:61–68.
13. Laarman GJ, Niemeyer MG, van der Wall EE, et al. Dipyridamole thallium testing: noncardiac side effects, cardiac side effects, electrocardiographic changes and hemodynamic changes after dipyridamole infusion with and without exercise. *Int J Cardiol* 1988;20:231–238.
14. Walker PR, James MA, Wilde RPH, Wood CH, Rees JR. Dipyridamole combined with exercise for thallium-201 myocardial imaging. *Br Heart J* 1986;55:321–329.

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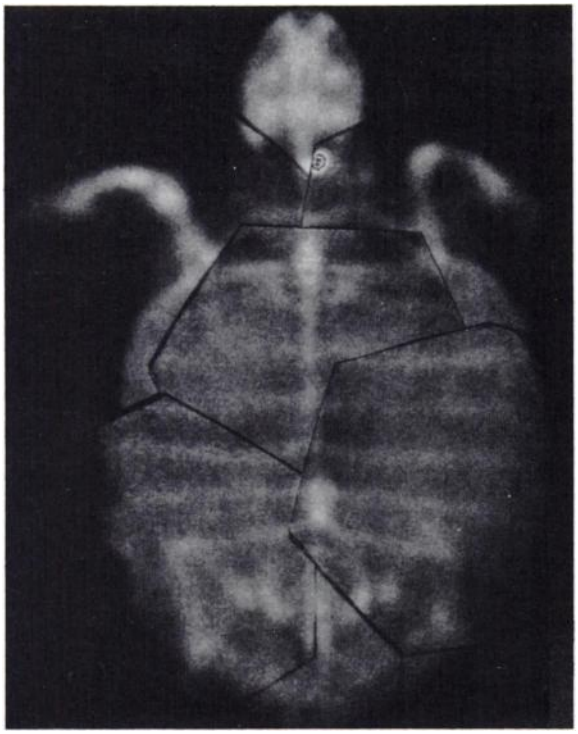

FIRST IMPRESSIONS

PURPOSE
The turtle was subject to progressive softening of its shell while in captivity and was evaluated using CT, plain films and a ^{99m}Tc-MDP (50 mCi) bone scan. The plain film revealed general osteopenia of the appendicular skeleton and a fracture of the proximal humerus of the right flipper. CT revealed near total demineralization of the shell. The bone scan shows inflammation near the site of the fracture (shown on the left side), but no increased uptake in the broken bone. In addition, the softened shell of the animal shows only blood-pool levels of MDP.

TRACER
^{99m}Tc-MDP

ROUTE OF ADMINISTRATION
Intravenously (into neck sinus, some extravasation visible)

TIME AFTER INJECTION
7 hr

INSTRUMENTATION
Gamma camera and x-ray

CONTRIBUTORS
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INSTITUTION
Suffolk University, New England Aquarium and Massachusetts General Hospital, Boston, Massachusetts