Comparison of Treadmill Exercise Versus Dipyridamole Stress With Myocardial Perfusion Imaging Using Rubidium-82 Positron Emission Tomography

Benjamin J. W. Chow, MD, FACC, Karthikeyan Ananthasubramaniam, MD, FACC, Robert A. deKemp, PhD, Mary M. Dalipaj, MRT(N), Rob S. B. Beanlands, MD, FACC, Terrence D. Ruddy, MD, FACC

Ottawa, Ontario, Canada

OBJECTIVES
This study assessed the feasibility of treadmill exercise rubidium-82 (82Rb) positron emission tomography (PET) and compared image quality and diagnostic content with dipyridamole 82Rb PET in patients referred for evaluation of coronary artery disease (CAD).

BACKGROUND
Dipyridamole stress 82Rb PET myocardial perfusion imaging (MPI) is an accurate imaging modality used to diagnose CAD and determine prognosis. Although pharmacologic stress is used routinely, exercise treadmill stress may be an alternative and provide clinical information helpful to decision making, particularly for patients unwilling or unable to tolerate pharmacologic stress.

METHODS
Fifty patients (mean age, 60 ± 10 years; 47 men) underwent treadmill exercise and dipyridamole 82Rb PET. Images were assessed: 1) qualitatively using a 17-segment model and a semiquantitative visual score on a five-point scale and with calculation of summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS); and 2) quantitatively with a 70% threshold for abnormal perfusion and expressed as extent of abnormal perfusion (% left ventricular).

RESULTS
Treadmill exercise was preferred by 74% of patients (37 of 50, p < 0.001). The exercise and dipyridamole 82Rb PET summed scores and quantitative extent of abnormal perfusion were very similar and highly correlated. Results of Bland-Altman analysis showed no significant bias. Image quality was superior with exercise stress with greater myocardial uptake and higher target to background ratios.

CONCLUSIONS
Treadmill exercise 82Rb PET is feasible and provides imaging results of similar diagnostic content and superior image quality compared with dipyridamole stress. Treadmill exercise is a reasonable alternative to pharmacologic stress with 82Rb PET MPI. (J Am Coll Cardiol 2005;45:1227–34) © 2005 by the American College of Cardiology Foundation

Dipyridamole stress positron emission tomographic (PET) myocardial perfusion imaging (MPI) is a highly sensitive and specific noninvasive modality for detection of coronary artery disease (CAD) (1–6). The superior diagnostic accuracy of PET relative to conventional gamma camera imaging is largely attributable to accurate attenuation correction and greater camera sensitivity.

Exercise is a safe physiologic stress, and exercise testing permits correlation of symptoms with exertion, measurement of exercise capacity and functional status, and assessment of efficacy of medical therapy. Experience with exercise testing with PET has been limited. Supine bicycle ergometry has been used successfully with rubidium-82 (82Rb) PET (7) but has not been adopted into clinical practice. Treadmill exercise results in a greater exercise workload than bicycle stress and is used more widely in North America. Patients unwilling or unable to tolerate pharmacologic stress may be candidates for exercise stress.

Although 13N-ammonia and 15O-H2O are available for PET MPI, clinical availability has been limited by the need for on-site cyclotrons. Rubidium-82, a generator-produced radioisotope, is commonly used for MPI. The short half-life of 82Rb (76 s) minimizes the time required for rest and stress imaging but has made its use with treadmill exercise stress logistically difficult.

To our knowledge, 82Rb PET MPI has never been combined with exercise treadmill stress testing. The objective of this study was to determine the feasibility of 82Rb PET MPI with treadmill exercise stress and to compare image quality and diagnostic content with dipyridamole PET MPI.
would you prefer?" two tests repeated (exercise or drug stress PET) which of stress using the question: "If you had to have one of the patients were questioned regarding their preferred modality of both dipyridamole and treadmill exercise, PET was excluded. The order of dipyridamole versus exercise stress for 6 h or longer before each study. Patients with derivatives, and atrioventricular (AV) nodal blocking drugs on a different day. The PET images were acquired with an ECAT ART whole body scanner (Siemens/CTI, Knoxville, Tennessee) equipped with 24 detector rings allowing the acquisition of 47 contiguous transaxial slices. The same imaging protocol was used for rest and stress imaging. A four-min cesium-137 transmission scan was acquired to confirm proper patient positioning and for attenuation correction (9). Chest markings with dye and the field of view positioning lasers of the PET camera ensured accurate repositioning of patients. After acquisition of transmission data, 10 to 35 mCi (370 to 1,295 MBq) of $^{82}$Rb was infused over 30 s at rest (or with stress as described in the subsequent text) and followed by a saline flush over 1 min using a custom infusion system. A 10-min dynamic acquisition was obtained, and static uptake images were created by summing the last 7.5 min of dynamic data. After rest imaging, an additional 10 min was allowed for decay of the $^{82}$Rb between rest and stress imaging. A post-test 4-min transmission scan was acquired for attenuation correction after the stress exercise and dipyridamole scans. All images were reconstructed using filtered backprojection with a Hann window cut-off of 18 mm and using scatter and attenuation correction.

**METHODS**

**Study population and design.** Between November 2001 and March 2003, 53 patients were prospectively enrolled into this single-center single-blinded study for comparison of exercise versus dipyridamole stress PET MPI. A second group of 15 patients underwent two serial rest and dipyridamole stress PET MPI studies for determination of the repeatability of dipyridamole stress PET MPI for comparison with the observed differences of exercise versus dipyridamole stress PET MPI. The total study population included 68 patients. All patients had either documented CAD or an intermediate (20% to 80%) to high pre-test probability (>80%) for CAD using Diamond and Forrester criteria (8). All patients were referred for dipyridamole PET MPI for diagnosis of CAD or to determine prognosis. Exclusion criteria included inability to give informed consent; age <18 years; inability to exercise on a treadmill; contraindication to dipyridamole such as asthma, bronchospasm, or theophylline dependence; or contraindication to radiation exposure such as pregnancy or breastfeeding, ongoing enrollment in other research involving radiation, or occupational radiation exposure. All patients gave informed consent to participate in the study. The study protocol was approved by the University of Ottawa Heart Institute Human Research Ethics Board.

Each patient underwent rest and dipyridamole stress PET MPI on one day and rest and exercise stress PET MPI on a different day. Patients abstained from caffeine, xanthine derivatives, and atrioventricular (AV) nodal blocking drugs for 12 h or longer and remained fasting except for medications for 6 h or longer before each study. Patients with changes in anginal pattern or cardiac medications between the dipyridamole and exercise PET MPI studies were excluded. The order of dipyridamole versus exercise stress was determined by availability of resources. Upon completion of both dipyridamole and treadmill exercise, PET patients were questioned regarding their preferred modality of stress using the question: “If you had to have one of the two tests repeated (exercise or drug stress PET) which would you prefer?”

**PET imaging.** Positron emission tomography MPI imaging was carried out at rest and with dipyridamole stress on one day and then repeated at rest and with exercise stress on a different day. The PET images were acquired with an ECAT ART whole body scanner (Siemens/CTI, Knoxville, Tennessee) equipped with 24 detector rings allowing the acquisition of 47 contiguous transaxial slices. The same imaging protocol was used for rest and stress imaging. A four-min cesium-137 transmission scan was acquired to confirm proper patient positioning and for attenuation correction (9). Chest markings with dye and the field of view positioning lasers of the PET camera ensured accurate repositioning of patients. After acquisition of transmission data, 10 to 35 mCi (370 to 1,295 MBq) of $^{82}$Rb was infused over 30 s at rest (or with stress as described in the subsequent text) and followed by a saline flush over 1 min using a custom infusion system. A 10-min dynamic acquisition was obtained, and static uptake images were created by summing the last 7.5 min of dynamic data. After rest imaging, an additional 10 min was allowed for decay of the $^{82}$Rb between rest and stress imaging. A post-test 4-min transmission scan was acquired for attenuation correction after the stress exercise and dipyridamole scans. All images were reconstructed using filtered backprojection with a Hann window cut-off of 18 mm and using scatter and attenuation correction.

**Dipyridamole stress testing.** Dipyridamole (0.14 mg/kg/min) was infused over five min. Heart rate and blood pressure were measured every three min, and electrocardiography (ECG) was monitored continuously. Eight min after initiation of dipyridamole infusion, $^{82}$Rb was administered. Image acquisition began with the onset of $^{82}$Rb infusion. A 10-min dynamic acquisition was obtained, and static uptake images were created by summing the last 7.5 min of dynamic data. Aminophylline (2 mg/kg) was infused 12 min after initiation of dipyridamole infusion.

**Exercise stress testing.** The Bruce protocol was used for the treadmill exercise protocol. Age-predicted maximal heart rate (APMHR) was estimated by 220 — age (10). Heart rate and blood pressure were measured every three min, and ECG was monitored continuously. During the last 1.5 min of peak exercise the patient received $^{82}$Rb intravenously. Upon completion of the treadmill exercise, the patient was repositioned in the PET scanner approximately three min after the onset of $^{82}$Rb infusion. A 7.5-min summed static uptake PET image was acquired.

**ECG and image analysis.** Positive ST-segment depression was defined as ≥1 mm horizontal or downsloping ST-segment depression at the J point persisting 80 ms beyond the J point or ≥1.5 mm upsloping depression at 80 ms beyond the J point (11). In patients with heart rates ≥135 beats/min, ST-segment measurements were performed 60 ms beyond the J point (11).

The PET images were assessed qualitatively by two expert observers blinded to the modality of stress and using

**Abbreviations and Acronyms**

APMHR = age-predicted maximum heart rate
AV = atrioventricular
CAD = coronary artery disease
CCS = Canadian Cardiovascular Society
ECG = electrocardiography
LV = left ventricular
MPI = myocardial perfusion imaging
PET = positron emission tomography
$^{82}$Rb = rubidium-82
SDS = summed difference score
SSS = summed stress score
SS = summed rest score

**Notes**

1. Heart rate (APMHR) was estimated by $220 - age (10). Heart rate and blood pressure were measured every three min, and electrocardiography (ECG) was monitored continuously. Eight min after initiation of dipyridamole infusion, $^{82}$Rb was administered. Image acquisition began with the onset of $^{82}$Rb infusion. A 10-min dynamic acquisition was obtained, and static uptake images were created by summing the last 7.5 min of dynamic data. Aminophylline (2 mg/kg) was infused 12 min after initiation of dipyridamole infusion.

2. Exercise stress testing. The Bruce protocol was used for the treadmill exercise protocol. Age-predicted maximal heart rate (APMHR) was estimated by $220 - age (10). Heart rate and blood pressure were measured every three min, and ECG was monitored continuously. During the last 1.5 min of peak exercise the patient received $^{82}$Rb intravenously. Upon completion of the treadmill exercise, the patient was repositioned in the PET scanner approximately three min after the onset of $^{82}$Rb infusion. A 7.5-min summed static uptake PET image was acquired.

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4. The PET images were assessed qualitatively by two expert observers blinded to the modality of stress and using
were positioned using the same locations: myocardium as slices of the myocardium, regions of interest for each patient and myocardium/blood pool) (14–16). Using transaxial (myocardium/lung, myocardium/gut, myocardium/liver, perfusion (13).

Preliminarily by a sectored analysis approach for rest and stress summed rest score (SRS), and summed difference score of radiotracer uptake) (12). Summed stress score (SSS), normal radiotracer uptake, 1/

Patient population. We prospectively enrolled 53 patients who underwent both treadmill exercise and dipyridamole stress 82Rb PET. One patient was excluded for premature termination of exercise (before 82Rb infusion). Two patients were excluded for significant changes in symptoms of angina between the two studies. One patient had worsening angina class (Canadian Cardiovascular Society [CCS] class 2 to 3). One patient had improvement in angina class (CCS class 3 to 1). The remaining 50 patients (mean age 60 ± 10 years; 47 men) completed the study and underwent both treadmill exercise and dipyridamole stress 82Rb PET. Thirty-seven (74%) patients had documented history of CAD (27 patients had a history of myocardial infarction, 29 had

**Table 1.** Dipyridamole and Exercise Treadmill Stress Clinical and ECG Data

<table>
<thead>
<tr>
<th></th>
<th>Dipyridamole</th>
<th>Exercise</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest HR (beats/min)</td>
<td>59 ± 10</td>
<td>64 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Rest systolic BP (mm Hg)</td>
<td>144 ± 27</td>
<td>139 ± 19</td>
<td>NS</td>
</tr>
<tr>
<td>Rest diastolic BP (mm Hg)</td>
<td>76 ± 12</td>
<td>77 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Rest HR-BP product</td>
<td>8,982 ± 2,433</td>
<td>8,895 ± 1,819</td>
<td>NS</td>
</tr>
<tr>
<td>Peak HR (beats/min)</td>
<td>79 ± 16</td>
<td>145 ± 20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak systolic BP (mm Hg)</td>
<td>139 ± 22</td>
<td>182 ± 26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak diastolic BP (mm Hg)</td>
<td>74 ± 11</td>
<td>87 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak HR × pressure</td>
<td>11,087 ± 3,462</td>
<td>26,519 ± 5,372</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with STD</td>
<td>14 (28%)</td>
<td>31 (62%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum STD (mm)</td>
<td>0.5 ± 1.0</td>
<td>1.3 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with ST-segment elevation</td>
<td>1/4</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Patients with chest pain</td>
<td>31 (62%)</td>
<td>19 (38%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Patient stress preference</td>
<td>13 (26%)</td>
<td>37 (74%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BP = blood pressure; ECG = electrocardiographic; HR = heart rate; HR × pressure = rate-pressure product; STD = ST-segment depression.

a 17-segment model and a five-point grading system (0 = normal radiotracer uptake, 1 = mildly reduced, 2 = moderately reduced, 3 = severely reduced, and 4 = absence of radiotracer uptake) (12). Summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) were calculated. Images were also analyzed quantitatively by a sectored analysis approach for rest and stress defect size using a 70% threshold cut-off for abnormal perfusion (13).

Image quality was assessed with criteria based on myocardial count density (Bq/cc) and target: background ratios (myocardium/lung, myocardium/gut, myocardium/liver, and myocardium/blood pool) (14–16). Using transaxial slices of the myocardium, regions of interest for each patient were positioned using the same locations: myocardium as myocardial region with the highest counts, lung as a 31 × 43-voxel triangular area in the left lung, gut as a 6 × 6-voxel area over the gut activity closest to the myocardium, liver as a 11 × 16-voxel area in the right upper lobe of the liver, and blood pool as a circular region with a diameter of 10 voxels in the center of the left ventricular (LV) cavity.

**Statistical analysis.** Statistical analysis was done using SPSS version 11.5 (Chicago, Illinois). Paired continuous variables were evaluated using the $t$ test, and noncontinuous variables with chi-square testing. The concordance of the observer grading of the exercise and dipyridamole stress scans was evaluated by calculating Kappa scores. Perfusion defects estimated as summed scores and %LV defect from the exercise and dipyridamole stress studies were correlated using a Pearson correlation coefficient and Bland-Altman plot analyses (17). Repeatability of the exercise and dipyridamole stress studies was calculated using the repeatability coefficient (17) and compared with repeatability of two dipyridamole stress studies. The repeatability coefficient is twice the standard deviation of the differences between the initial and repeated tests (17).

**RESULTS**

**Table 2.** Dipyridamole and Exercise Treadmill Stress Image Data

<table>
<thead>
<tr>
<th></th>
<th>Dipyridamole</th>
<th>Exercise</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest $^{82}$Rb dose (MBq)</td>
<td>786 ± 206</td>
<td>770 ± 171</td>
<td>NS</td>
</tr>
<tr>
<td>Stress $^{82}$Rb dose (MBq)</td>
<td>789 ± 185</td>
<td>757 ± 188</td>
<td>NS</td>
</tr>
<tr>
<td>SRS</td>
<td>2.2 ± 3.7</td>
<td>2.1 ± 4.1</td>
<td>NS</td>
</tr>
<tr>
<td>SDS</td>
<td>7.2 ± 8.3</td>
<td>6.6 ± 7.7</td>
<td>NS</td>
</tr>
<tr>
<td>Rest defect (% LV)</td>
<td>5.0 ± 6.0</td>
<td>4.5 ± 5.3</td>
<td>NS</td>
</tr>
<tr>
<td>Rest myocardial uptake (Bq/cc)</td>
<td>4.6 ± 7.6</td>
<td>4.3 ± 7.9</td>
<td>NS</td>
</tr>
<tr>
<td>Stress myocardial uptake (Bq/cc)</td>
<td>15.2 ± 16.2</td>
<td>14.4 ± 16.0</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardium/lung rest</td>
<td>11,293 ± 3,668</td>
<td>12,192 ± 4,597</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardium/lung stress</td>
<td>14,476 ± 4,029</td>
<td>22,405 ± 10,747</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardium/gut rest</td>
<td>10.9 ± 4.8</td>
<td>12.4 ± 14.5</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardium/gut stress</td>
<td>23.4 ± 4.4</td>
<td>14.8 ± 9.3</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardium/liver rest</td>
<td>1.2 ± 0.7</td>
<td>1.1 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardium/liver stress</td>
<td>1.8 ± 1.5</td>
<td>5.1 ± 4.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardium/blood pool rest</td>
<td>3.8 ± 3.6</td>
<td>2.8 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardium/blood pool stress</td>
<td>3.4 ± 1.4</td>
<td>26.9 ± 66.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Myocardium/blood pool rest</td>
<td>2.5 ± 0.8</td>
<td>2.5 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardium/blood pool stress</td>
<td>3.0 ± 0.8</td>
<td>3.8 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LV = left ventricle; SDS = summed difference score; SRS = summed rest score; SSS = summed stress score.
previous revascularization with 27 having percutaneous coronary interventions and 9 having coronary artery bypass surgery). The remaining 13 (26%) patients had either intermediate or high pre-test probability for CAD. Cardiac risk factors included hypertension in 27 (54%), diabetes in 10 (20%), current smoking in 9 (18%), previous smoking in 30 (60%), family history of CAD in 17 (34%), and dyslipidemia in 39 (78%) patients. The second set of 15 patients (mean age 64 ± 14 years; 13 men) undergoing two serial rest and dipyridamole stress PET MPI studies for determination of the repeatability of dipyridamole stress PET MPI were similar to the 50 patients undergoing exercise and dipyridamole stress PET MPI.

**Stress testing.** The median time interval between treadmill exercise and dipyridamole stress studies was 6 days with a mean of 13 ± 26 days. Patients exercised an average of 8.4 ± 2.4 min. The mean % APMHR was 88 ± 11% with 37 (74%) patients achieving ≥85% APMHR. For exercise stress studies, mean time interval from onset of 82Rb infusion to initiation of acquisition of emission data was 3.0 ± 0.5 min.

Exercise and dipyridamole stress test results are compared in Table 1. Peak heart rate, blood pressure, and rate-pressure product were significantly greater with exercise than dipyridamole stress. ST-segment depression was more common and in more leads with treadmill exercise than dipyridamole stress. Conversely, chest pain was more frequent with dipyridamole versus treadmill exercise stress. More patients preferred treadmill exercise over dipyridamole stress. Of the 13 patients with submaximal exercise stress, 6 discontinued exertion due to chest pain, 5 due to fatigue, and 2 due to dyspnea.

**MPI.** The SSS, SRS, SDS, and quantitative defect sizes with dipyridamole versus exercise stress 82Rb PET MPI

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Figure 1. Summed scores for dipyridamole and exercise treadmill stress images: (A) summed stress score; (B) summed rest score; (C) summed difference score.

Figure 2. Quantitative perfusion defect size (% left ventricle) for dipyridamole and exercise treadmill stress images: (A) summed stress score; (B) summed rest score.
were very similar (Table 2) and highly correlated (Figs. 1 and 2). One patient had a significant discrepancy between exercise SSS (0.75) and dipyridamole SSS (12.5). During exercise, this patient had a significant drop in systolic blood pressure of 30 mm Hg, which may have resulted in global myocardial hypoperfusion and less marked heterogeneity in myocardial perfusion (Figs. 3 and 4).

Bland-Altman analysis (Fig. 5, Table 3) for the SSS, SRS, SDS and quantitative defect sizes (dipyridamole vs. exercise stress Rb PET MPI) showed no significant bias with the mean of the differences similar to zero and no systematic overestimation or underestimation. In addition, agreement between dipyridamole versus exercise stress Rb PET MPI was similar to the agreement observed between repeated dipyridamole stress Rb PET MPI studies (Table 3). Repeatability coefficients for dipyridamole versus exercise stress Rb PET MPI data were similar to results with repeated dipyridamole stress Rb PET MPI studies (Table 3). Kappa scores assessing concordance for categories of normal/equivocal versus abnormal for the exercise versus dipyridamole SSS and SRS were good to very good on a patient level (0.72 and 0.85, respectively; Table 4) and by coronary artery territories (left anterior descending 0.72 and 0.58, left circumflex 0.72 and 0.78, right coronary 0.71 and 0.75, respectively).

Because some of the variability between dipyridamole versus exercise stress may be related to submaximal exercise stress, an analysis of SSS and stress defect (% LV) was performed in patients (n = 13) with submaximal exercise stress (heart rate <85% APMHR). The SSS (5.8 ± 5.5, 5.1 ± 5.9, respectively; p = NS) and quantitative defect sizes (14.1 ± 15.0, 13.9 ± 17.0, respectively; p = NS) with dipyridamole versus exercise stress were very similar and highly correlated (r = 0.96, p < 0.001 and r = 0.96, p < 0.001, respectively).

Myocardial Rb uptake was significantly greater with exercise compared with dipyridamole stress (Table 2). Higher ratios of myocardial uptake to gut, liver, and blood pool uptake were observed with exercise stress compared with dipyridamole stress (Table 2).
DISCUSSION

This study demonstrates that treadmill exercise $^{82}$Rb PET MPI is feasible. The diagnostic content of the images and repeatability is very similar to dipyridamole $^{82}$Rb PET MPI. In addition, the image quality associated with treadmill exercise is better than with dipyridamole stress.

Exercise treadmill stress has proven to be safe in all ages (18) and yields additional information unobtainable with pharmacologic stress. Exercise treadmill stress quantifies exercise capacity and functional status, correlates symptoms with exertion, assesses the effectiveness of medical therapy, and may provide prognostic information (19). In this study, patients preferred treadmill exercise to dipyridamole stress.

Previous studies have found similar sensitivity (60% to 94% vs. 48% to 100%) and specificity (68% to 100% vs. 64% to 100%) of exercise and dipyridamole thallium–201 and technetium–99m single photon emission computed tomography in detecting significant coronary stenoses (20,21). However, one study found that dipyridamole thallium–201 may be more sensitive than exercise thallium–201 (70% vs. 52%) in detecting coronary stenoses between 40% and 60% (21). Similar diagnostic results with myocardial perfusion imaging after dipyridamole and exercise stress suggest that radiotracer uptake is also similar. However, changes in coronary blood flow induced by exercise and dipyridamole differ with increases in normal coronary arteries by exercise of 100% to 300% and dipyridamole of 400% (22). In addition, impaired vasodilation with dipyridamole has been shown (23) and may partially explain the greater myocardial uptake of $^{82}$Rb after exercise observed in this study.

Supine bicycle exercise PET has been performed successfully (7,24,25) and permits dynamic data acquisition with some potential patient motion during emission data acquisition. Although exercise stress PET has not been adopted into common practice in North America, exercise treadmill stress is commonly used and readily available. Dynamic data acquisition is not possible with treadmill exercise stress, and treadmill exercise has not been performed previously with $^{82}$Rb PET. Camici et al. (7) found that areas of reduced $^{82}$Rb uptake returned to control values after 5 to 14 min after the end of bicycle exercise, which may limit the time available for emission acquisition. In our study, 3.0 min were required for $^{82}$Rb infusion, saline flush, termination of treadmill exercise, and repositioning in the PET camera. Image acquisition required an additional 7.5 min. Thus, a total of 10.5 min was required for image acquisition with the treadmill $^{82}$Rb PET MPI protocol.

Variability between treadmill exercise and dipyridamole stress defect size studies may be explained partially by the variability of the time intervals from $^{82}$Rb infusion and beginning of image acquisition. The larger stress defect sizes observed in some patients with exercise may have been related to submaximal vasodilation with dipyridamole or illicit ingestion of caffeine. Although submaximal exercise stress may lead to an underestimation of the extent of ischemia, similar SSS and quantitative defect sizes were observed in the subgroup analysis of patients with submaximal exercise.

Repeatability of exercise $^{82}$Rb PET MPI was not evaluated specifically. However, the differences between exercise and dipyridamole $^{82}$Rb PET MPI were compared with the repeatability of dipyridamole $^{82}$Rb PET MPI and found to be very similar.

The image quality with treadmill exercise was superior to dipyridamole stress images with higher ratios of myocardial uptake to gut and liver uptake after exercise stress and was possibly related to increased sympathetic tone and reduction of splanchnic blood flow as previously reported with dipyridamole thallium imaging (15). The higher ratio of myo-
cardiac uptake to blood pool uptake after exercise stress may be related to the 30-s delay in acquisition of the exercise images and more time for blood pool clearance.

Our clinical experience with treadmill exercise stress $^{82}$Rb PET was very positive but did present technical challenges. After treadmill exercise stress, extra care had to be taken with repositioning the patient in the PET scanner to ensure that the patient’s heart was within the field of view of the PET camera. The chest of each patient was marked with blue dye, and patients were repositioned after exercise by aligning the chest markings with the laser system of the camera. The treadmill had to be adjacent to the PET camera to expedite immediate imaging and ECG monitoring. In addition, differences in breathing between the emission and transmission images may lead to errors in registration of the images and alter perfusion particularly in the inferior wall. However, careful review of patient images did not identify any patients with apparent misregistration, and there were no statistically significant differences in perfusion defects in the inferior wall between dipyridamole and exercise stress.

Rubidium-$^8$Rb is a radiotracer that can be used in centers without immediate access to a cyclotron. The short half-life of $^{82}$Rb has both benefits and detriments when used in MPI. The very short half-life reduces overall test duration. However, its short half-life also limits the time available for emission image acquisition and requires rapid patient transfer from the treadmill to the PET camera. $^{13}$N-ammonia has several benefits over $^{82}$Rb and may be an ideal radiotracer to be used in conjunction with treadmill exercise PET. $^{13}$N-ammonia’s longer half-life (10 min) would eliminate the time constraints encountered with $^{82}$Rb. As a bolus infusion, it would reduce infusion time and allow its infusion to be temporally closer to peak exercise. In addition, $^{13}$N-ammonia has lower positron energy than $^{82}$Rb and may result in better image quality and resolution.

**CONCLUSIONS**

Treadmill exercise $^{82}$Rb PET is feasible and provides imaging results of similar diagnostic content and better quality compared with dipyridamole stress. In our study, treadmill exercise stress was preferred over dipyridamole stress by patients who can exercise. The option of treadmill exercise PET can be now considered in patients requiring evaluation of CAD.

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**Reprint requests and correspondence:** Dr. Terrence D. Ruddy, University of Ottawa Heart Institute, 40 Ruskin Street (H-1 PET Centre), Ottawa, ON K1Y 4W7 Canada. E-mail: truddy@ottawaheart.ca.

**REFERENCES**