ABSTRACT

OBJECTIVES The goal of this study was to compare regadenoson and dipyridamole hyperemia for quantitative myocardial perfusion imaging.

BACKGROUND Regadenoson is commonly used for stress perfusion imaging. However, no study in nuclear cardiology has employed a paired design to compare quantitative hyperemic flow from regadenoson to more traditional agents such as dipyridamole. Additionally, the timing of regadenoson bolus relative to tracer administration can be expected to affect quantitative flow.

METHODS Subjects underwent 2 rest/stress cardiac positron emission tomography scans using an Rb-82 generator. Each scan employed dipyridamole and a second drug in random sequence, either regadenoson according to 5 timing sequences or repeated dipyridamole. A validated retention model quantified absolute flow and coronary flow reserve.

RESULTS A total of 176 pairs compared regadenoson (126 pairs, split unevenly among 5 timing sequences) or repeated dipyridamole (50 pairs). The cohort largely had few symptoms, only risk factors, and nearly normal relative uptake images, with 8% typical angina or dyspnea, 20% manifest coronary artery disease, and a minimum quadrant average of 80% (interquartile range: 76% to 83%) on dipyridamole scans. Hyperemic flow varied among regadenoson timing sequences but showed consistently lower stress flow and coronary flow reserve compared with dipyridamole. A timing sequence most similar to the regadenoson package insert achieved about 80% of dipyridamole hyperemia, whereas further delaying radiotracer injection reached approximately 90% of dipyridamole hyperemia. Because of the small numbers of pairs for each regadenoson timing protocol and a paucity of moderate or large perfusion defects, we did not observe a difference in relative uptake.

CONCLUSIONS With the standard timing protocol from the package insert, regadenoson achieved only 80% of dipyridamole hyperemia quantitatively imaged by cardiac positron emission tomography using Rb-82. A nonstandard protocol using a more delayed radionuclide injection after the regadenoson bolus improved its effect to 90% of dipyridamole hyperemia. (J Am Coll Cardiol Img 2015;8:438–47) © 2015 by the American College of Cardiology Foundation. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Diagnostic coronary vasodilation provides insights into the cardiac response to stress in a controlled test. Potential abnormalities include a perfusion deficit, wall motion abnormality, intracoronary pressure gradient (fractional flow reserve [FFR]) or flow increase (coronary flow reserve [CFR]), electrocardiographic changes, and clinical angina. Vasodilator stress mainly reflects the consequences of a structurally fixed coronary stenosis (1), compared with demand stress (exercise or dobutamine) that includes superimposed dynamic processes (vasoconstriction, tachycardia with shortened diastolic perfusion time, coronary vasospasm, and rare lumen compression from myocardial...
bridging or coronary anomalies). Because the vast majority of dynamic coronary disease can be treated medically, vasodilator stress offers a more specific tool for identifying patients who may benefit from revascularization of significant fixed disease.

After the first vasodilator stress imaging in 1978 with dipyridamole (2), it became widely available by 1995 (3) and adenosine by 1994 (4). A decade later, adenosine A2A receptor agonists were developed like binodenoson in 2004 (5), regadenoson in 2005 (6), and apadenoson around that time (NCT00990327), although currently only regadenoson has regulatory approval. Although dipyridamole, adenosine, and regadenoson offer tradeoffs in terms of cost, infusion duration, and side-effect profile, the key diagnostic question remains the degree of hyperemia. A lesser hyperemic stimulus underestimates physiologic stenosis severity.

Currently, regadenoson enjoys its largest market for myocardial perfusion imaging. Existing studies in this area comparing it with established vasodilators have never employed a paired design with absolute flow quantification. Therefore, we used cardiac positron emission tomography (PET) to compare the degree of hyperemia between regadenoson and dipyridamole. Additionally, we explored the timing effect of radiotracer injection following the regadenoson bolus.

METHODS

We performed an investigator-initiated, single-center, diagnostic accuracy study at the Weatherhead PET Center for Preventing and Reversing Atherosclerosis of the University of Texas Medical School at Houston and Memorial Hermann Hospital. Subjects gave written informed consent as approved by the institutional review board and underwent enrollment between December 2012 and June 2014. Subjects at least 40 years or older were recruited by convenience via several routes: volunteers not meeting entry criteria for our ongoing randomized Century trial (NCT00756379), patients referred for a medical indication, and word of mouth. Exclusion criteria included any absolute contraindication to dipyridamole or regadenoson, pregnancy or active breastfeeding, current participation in another clinical research study, and inability to undergo 2 PET scans within 2 months, but at least 1 day apart. Subjects were instructed not to change medications or have invasive procedures between the 2 PET scans.

The vast majority of subjects received 2 different vasodilators. Assignment of subjects to drug sequence (dipyridamole then regadenoson, or regadenoson then dipyridamole) was performed by the nuclear medicine technologist at the time of the first PET scan by using a coin flip for 1:1 randomization. Investigators, study subjects, and PET center staff performing imaging were not blinded to vasodilator assignment. A minority of subjects received dipyridamole for both scans to quantify its test/retest repeatability. Eleven subjects could not complete both scans and were excluded from the analysis. To screen for drugs that might affect vasodilation, serum and urine samples at each PET scan were tested for caffeine, nicotine, and nicotine’s metabolite cotinine.

A sample size of about 50 complete pairs was estimated based on a paired test with \( \alpha = 0.05 \), \( \beta = 0.80 \), variance in stress flow of 0.37 to 0.50, variance in CFR of 0.80 to 0.94 (both derived from our previous work), and the desire to detect differences between 0.2 and 0.5 in stress flow and CFR. After completely enrolling and analyzing this first timing sequence, we decided to study additional timing sequences to construct a response curve. Each timing sequence had a pre-specified sample size based on the variance observed in the first sequence. Therefore, our study consisted of serial mini-trials, each performed and primarily analyzed separately.

CARDIAC PET ACQUISITION AND ANALYSIS. Our imaging protocol has been described previously, and this section follows previous publications closely (7). Subjects were instructed to fast for 4 h and abstain from caffeine, theophylline, and cigarettes for 24 h. Cardiac PET was performed using a Discovery ST 16-slice PET-CT scanner (GE Healthcare, Waukesha, Wisconsin) in 2-dimensional mode with settings for an in-plane resolution of approximately 6 to 7 mm full-width at half-maximum.

Rest emission images were obtained over 7 min beginning immediately upon intravenous injection of 30 to 50 mCi of generator-produced Rb-82 (Bracco Diagnostics, Princeton, New Jersey). The first 2 min during emission were binned to form the arterial input image. The last 5 min during emission were binned to form the myocardial uptake image. After completion of the resting scan, pharmacological stress was performed as detailed in the following text, and the same dose of radiotracer was injected. Stress emission images were acquired for 7 min and...
binned into arterial and myocardial images as for the resting scan.

Severe angina relieved only after intravenous aminophylline or theophylline, sublingual nitroglycerin, and/or intravenous metoprolol was noted, distinct from common and nonischemic vasodilator-induced chest symptoms treated routinely with xanthine derivatives. Continuous 12-lead electrocardiographic monitoring during stress identified significant, >1-mm ST-segment depression. Hemodynamic parameters of heart rate and blood pressure were recorded at the time of both tracer injections.

Computed tomography (CT) scans for attenuation correction were acquired before rest and after stress emission imaging and have been previously reported (8). Fusion images superimposed PET emission and CT transmission scans in horizontal, coronal, and sagittal views. Coregistration was optimized by shifting as needed. PET images were reconstructed using filtered back-projection with a ramp filter (cutoff 6.5 mm) and then post-processed by a fifth-order Butterworth filter (cutoff 0.50 cycles/cm). After attenuation correction and reconstruction, transaxial PET images were exported for analysis on CARDIAC software (version 4.66, Positron Corporation, Westmont, Illinois) to generate true short- and long-axis views, perpendicular and parallel to the long axis of the left ventricle (LV). Circumferential profiles of maximum radial activity for each true short-axis slice were used to construct 2-dimensional topographic views of the LV.

Four basal slices were not used for quantitative analysis because of low counts in the membranous interventricular septum. Two apical slices were not used for quantitative analysis because of potential partial volume errors and apical motion. Combined size and severity of perfusion defects was quantified by 2 metrics: first, the percentage of the LV with relative activity <60% of maximum activity (100%), which is >6 SD below mean activity in normal volunteers (7); and, second, the value in the quadrant with the lowest average relative uptake (minimum quadrant average).

For each radial segment of every short-axis slice, our experimentally validated model (9) implemented using commercial software (10) quantified absolute myocardial flow. The flow model does not use time-activity curves, but instead, integrates arterial input and myocardial uptake over the first 2 and next 5 min, respectively, after tracer injection. Our flow model has also been used by others (11), who reported it to “have higher sensitivity for detection and localization of abnormal flow” (12) than time Activity curve models (13) that we consider less suited for routine clinical application, as in our daily practice for over 7 years.

The topographic map of absolute flow was smoothed using a 5-by-5 pixel average to suppress imaging noise. CFR was computed as the stress-to-rest ratio on a pixel basis. We employ the term CFR instead of myocardial flow reserve to emphasize the general physiological principle independent of measurement technique. Arterial inputs were customized from among the aortic and left atrium locations as previously detailed (14).

**VASODILATOR STRESS PROTOCOLS.** Dipyridamole (142 µg/kg/min) was infused for 4 min. Four min after the completion of dipyridamole infusion, the Rb-82 generator was activated.

Figure 1 displays the 5 different regadenoson timing protocols. The sequence of Rb-82 generator activation, radiotracer delivery, and PET scanner imaging remained the same in all cases. However, the temporal difference between the regadenoson bolus and Rb-82 generator activation varied. A single-use, pre-filled, 5-ml syringe of regadenoson 0.4 mg was administered as a 10-s injection via peripheral vein, followed by a 5-ml flush.

Timing protocol B in Figure 1 corresponds to the package insert instructions to “administer the radionuclide myocardial perfusion imaging agent 10 to 20 s after the saline flush” (15). Note that the name for protocol B in other figures and tables as +10 s refers to the time from starting the regadenoson bolus to activating the Rb-82 generator. Although the exact radiotracer delivery start time after activation varied slightly among generators, typically it took approximately 10 to 15 s to begin.

**STATISTICAL ANALYSIS.** We used R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria) and employed standard summary statistical tests. Applicable tests were 2-tailed, and p < 0.05 was considered statistically significant. Minimum quadrant average and percentage of the LV below 60% of maximum were found to be sufficiently non-normal on inspection of quantile-quantile plots. Analysis of variance (ANOVA) compared characteristics among the timing protocols. Paired t tests or Wilcoxon signed rank tests compared flow and uptake endpoints between scans in the same subject. A McNemar test compared binary regadenoson and dipyridamole effects.

An ANOVA model with mixed effects (to account for repeated measurements from the same subject) compared absolute flow and CFR among the 5 regadenoson timing sequences (−15, +10, +40, +55, and +80 s). If an overall ANOVA p value was
Each row represents a different timing sequence, depicting time along the x-axis for 3 different components: regadenoson administration (top line), Rb-82 generator activation and radiotracer infusion (teal dot along middle line), and positron emission tomography (PET) imaging (bottom line). Thick black lines denote activity on the thin gray timelines. The regadenoson bolus lasted 10 s for all protocols, followed by a 5-ml saline flush. Typically, 10 to 15 s elapsed between generator activation and radiotracer injection, here denoted as a fixed 15-s interval. PET imaging began coincident with radiotracer infusion and occurred in 2 sequential components: a 2-min arterial phase followed immediately by a 5-min myocardial phase. The pink arrow and text for each sequence gives the time between starting the regadenoson bolus and activating the generator.
significant, then a Tukey all-pair comparison was applied to determine which conditions provided a different response. To explore for a potential differential effect of body mass index on absolute flow or CFR, we employed a mixed-effects ANOVA model that adjusted for its value at rest, hyperemia, and CFR (both).

**RESULTS**

Table 1 lists the clinical and hemodynamic characteristics of the participants with complete pairs. The median time between scans was 14 (interquartile range [IQR]: 7 to 21) days. Eleven additional subjects

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**TABLE 1**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All Pairs</th>
<th>Repeat Dipyridamole</th>
<th>Regadenoson +15 s</th>
<th>Regadenoson +10 s</th>
<th>Regadenoson +40 s</th>
<th>Regadenoson +55 s</th>
<th>Regadenoson +80 s</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Pairs</td>
<td>176</td>
<td>50</td>
<td>15</td>
<td>50</td>
<td>31</td>
<td>15</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>60 ± 9</td>
<td>62 ± 10</td>
<td>64 ± 8</td>
<td>57 ± 10</td>
<td>61 ± 7</td>
<td>60 ± 10</td>
<td>58 ± 6</td>
<td>0.042</td>
</tr>
<tr>
<td>Male</td>
<td>126 (72)</td>
<td>38 (76)</td>
<td>12 (80)</td>
<td>35 (70)</td>
<td>13 (87)</td>
<td>16 (52)</td>
<td>12 (80)</td>
<td>0.13</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28 ± 5</td>
<td>28 ± 5</td>
<td>27 ± 5</td>
<td>28 ± 5</td>
<td>30 ± 4</td>
<td>28 ± 5</td>
<td>31 ± 6</td>
<td>0.29</td>
</tr>
</tbody>
</table>

**Risk factors and history**

Hypertension 79 (45) 22 (44) 10 (67) 20 (40) 7 (4) 14 (45) 6 (40) 0.63
Dyslipidemia 132 (75) 40 (80) 10 (67) 34 (68) 14 (93) 24 (77) 10 (67) 0.30
Diabetes mellitus 15 (9) 7 (14) 3 (20) 1 (7) 1 (3) 0 (0) 0.21
Tobacco (current or previous) 52 (30) 16 (32) 8 (5) 15 (28) 3 (13) 2 (6) 1 (7) 0.60
Previous invasive angiography 37 (21) 12 (24) 4 (7) 9 (18) 5 (33) 4 (7) 3 (20) 0.60
Previous PCI 27 (15) 8 (16) 5 (33) 7 (14) 3 (20) 1 (3) 3 (20) 0.11
Previous CABG 8 (5) 3 (6) 2 (13) 2 (4) 0 (0) 1 (3) 0 (0) 0.60
Previous MI 16 (9) 4 (8) 3 (20) 4 (8) 2 (13) 2 (6) 1 (7) 0.69

**Medications**

Statin 88 (50) 25 (50) 10 (67) 23 (46) 11 (73) 15 (48) 4 (27) 0.13
Antiplatelet 84 (48) 17 (34) 9 (60) 27 (54) 8 (53) 17 (55) 6 (40) 0.25
Beta-blocker 49 (28) 15 (30) 8 (53) 10 (20) 5 (33) 7 (23) 4 (27) 0.22
ACE-I or ARB 48 (27) 14 (28) 3 (20) 12 (24) 7 (47) 9 (29) 3 (20) 0.60
Calcium blocker 14 (8) 3 (6) 1 (7) 4 (8) 2 (13) 4 (13) 0 (0) 0.69
Diuretic 22 (12) 7 (14) 3 (20) 4 (8) 3 (20) 4 (13) 1 (7) 0.66
Nitrates 3 (2) 1 (2) 0 (0) 1 (2) 1 (7) 0 (0) 0 (0) 0.69

**Symptoms and EF**

Dyspnea 10 (6) 2 (4) 0 (0) 3 (6) 2 (13) 2 (6) 1 (7) 0.68
Nitroprusside 53 (3) 10 (18) 2 (4) 6 (12) 2 (13) 1 (7) 0 (0) 0.63

**LVEF (%)**

73 ± 8 72 ± 8 70 ± 10 73 ± 7 69 ± 8 76 ± 5 75 ± 8 0.031

**Dipyridamole hemodynamics**

Rest heart rate (beats/min) 63 ± 11 61 ± 10 60 ± 10 64 ± 11 64 ± 13 65 ± 12 66 ± 14 0.35
Rest systolic blood pressure (mm Hg) 115 ± 17 119 ± 19 116 ± 17 113 ± 6 114 ± 15 115 ± 16 115 ± 16 0.60
Rest diastolic blood pressure (mm Hg) 66 ± 10 68 ± 10 63 ± 10 64 ± 9 67 ± 14 64 ± 12 68 ± 6 0.33
Stress heart rate (beats/min) 89 ± 13 87 ± 13 83 ± 13 91 ± 13 92 ± 13 91 ± 13 93 ± 15 0.15
Stress systolic blood pressure (mm Hg) 119 ± 15 122 ± 17 111 ± 15 117 ± 15 121 ± 13 120 ± 15 120 ± 14 0.21
Stress diastolic blood pressure (mm Hg) 63 ± 10 64 ± 9 57 ± 12 62 ± 9 65 ± 14 64 ± 11 63 ± 8 0.21

**2nd drug (repeat dipyridamole or regadenoson) hemodynamics**

Rest heart rate (beats/min) 63 ± 12 60 ± 10 59 ± 8 65 ± 13 61 ± 9 67 ± 12 68 ± 15 0.023
Rest systolic blood pressure (mm Hg) 117 ± 17 117 ± 15 116 ± 18 117 ± 18 116 ± 24 117 ± 13 117 ± 14 1.00
Rest diastolic blood pressure (mm Hg) 67 ± 11 67 ± 9 63 ± 9 66 ± 13 68 ± 14 67 ± 9 70 ± 10 0.68
Stress heart rate (beats/min) 91 ± 15 85 ± 15 82 ± 12 96 ± 15 88 ± 11 98 ± 14 93 ± 13 <0.001
Stress systolic blood pressure (mm Hg) 120 ± 19 120 ± 14 111 ± 18 120 ± 22 114 ± 21 124 ± 19 122 ± 18 0.30
Stress diastolic blood pressure (mm Hg) 62 ± 12 64 ± 10 61 ± 14 60 ± 14 62 ± 14 62 ± 11 63 ± 9 0.66

Values are n, mean ± SD, or n (%).

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft surgery; EF = ejection fraction; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention.
were excluded because they only completed 1 PET scan for a variety of reasons: 6 had a severe clinical event or invasive procedure, 2 were unable to obtain intravenous access, 1 had bronchospasm from dipyridamole (successfully treated by aminophylline alone), and 2 had scheduling issues. Absolute rest and stress heart rates for regadenoson or repeat dipyridamole differed among the timing groups (p = 0.023 and p < 0.001, respectively). However, relative heart rate and blood pressure changes between rest and stress showed no significant differences among the various timing groups.

Figure 2 and Table 2 provide the absolute flow and CFR results. Resting flow did not vary between repeated dipyridamole scans or between dipyridamole and regadenoson under any timing protocol. However, stress flow and CFR were systematically lower for all regadenoson timing sequences but unchanged for repeat dipyridamole. The relationship between absolute stress flow and CFR versus timing sequence in Figure 2 demonstrates a rise/fall pattern such that stress flow and CFR were highest for the +55 s protocol (Rb-82 generator activated 55 s after the start—not end—of the 10 s regadenoson bolus).

Mixed-effects ANOVA demonstrated no significant difference in resting flow among the 5 regadenoson timing sequences (p = 0.12), whereas significant differences were noted for stress flow and CFR (both p < 0.001). The Tukey comparison demonstrated that regadenoson stress flow was lower than dipyridamole for the −15, +10, and +40 s timing sequences (all p ≤ 0.002), with nonsignificant trends for the +55 and +80 s timing sequences (p = 0.16 and p = 0.082, respectively). Stress flow was higher for the +55 sequence compared with −15 or +10 (both p ≤ 0.002), higher for +80 compared with −15 (p = 0.007), and borderline for +40 compared with −15 (p = 0.081). Similarly, the Tukey comparison found that regadenoson CFR was lower than dipyridamole for the −15, +10, and +55 timing sequences (p < 0.001) and borderline for +40 and +80 (p = 0.079 and p = 0.104, respectively). CFR was higher for the +40, +55, and +80 sequences compared with −15 (all p < 0.021).

No significant differential effect of body mass index on absolute flow or CFR was observed between regadenoson and dipyridamole (all p > 0.05 for an interaction). Rest PRP and dipyridamole flow were significantly, but weakly, correlated (r² = 0.21; p < 0.001), as were stress PRP and dipyridamole flow (r² = 0.15; p < 0.001), implying that PRP explains about 20% or less of the population variation in flow. The findings in Table 2 did not change significantly after adjusting for PRP. Injected Rb-82 dose did not differ systematically between dipyridamole and regadenoson (paired p > 0.99).

Overall, the cohort mostly demonstrated nearly normal stress images, with a median 0.4% (IQR: 0% to 2.3%) of the LV below 60% of maximum and minimum quadrant average of 80% (IQR: 76% to 83%) on dipyridamole scans. Consequently, each timing sequence contained very few abnormal scans. Taken together, these circumstances explain why paired comparisons for both relative uptake metrics showed no significant differences between dipyridamole or regadenoson for any timing sequence, despite a difference in the magnitude of hyperemia.

**Figure 2** Absolute Flow and Coronary Flow Reserve

(A to C) Each panel depicts the unitless flow ratio to baseline dipyridamole for the 5 regadenoson (Rega) timing sequences (labeled as “Rega X sec,” where the seconds correspond to the red text in Figure 1) and repeated dipyridamole (Dipy). Teal dots provide the raw data for each pair, whereas the solid pink bars and red numbers summarize the mean, and the thin pink bars mark 1 SD.
TABLE 2 Absolute Flow and CFR

<table>
<thead>
<tr>
<th>Pairing</th>
<th>Absolute Flow (ml/min/g) or CFR</th>
<th>( \Delta ) (Compared With Baseline Dipyridamole)</th>
<th>p Value (Paired t Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Stress</td>
<td>CFR</td>
</tr>
<tr>
<td>Dipyridamole (all)</td>
<td>NA</td>
<td>0.85 ± 0.25</td>
<td>2.27 ± 0.57</td>
</tr>
<tr>
<td>Repeat dipyridamole</td>
<td>50</td>
<td>0.81 ± 0.24</td>
<td>2.19 ± 0.61</td>
</tr>
<tr>
<td>Regadenoson - 15 s</td>
<td>15</td>
<td>0.76 ± 0.17</td>
<td>1.34 ± 0.36</td>
</tr>
<tr>
<td>Regadenoson - 10 s</td>
<td>50</td>
<td>0.81 ± 0.26</td>
<td>1.79 ± 0.44</td>
</tr>
<tr>
<td>Regadenoson - 40 s</td>
<td>15</td>
<td>0.76 ± 0.16</td>
<td>1.84 ± 0.45</td>
</tr>
<tr>
<td>Regadenoson - 55 s</td>
<td>31</td>
<td>1.04 ± 0.32</td>
<td>2.33 ± 0.57</td>
</tr>
<tr>
<td>Regadenoson - 80 s</td>
<td>15</td>
<td>0.91 ± 0.29</td>
<td>2.21 ± 0.47</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

CFR = coronary flow reserve.

Systematic caffeine and nicotine measurements detected 7 subjects with caffeine on both scans, 9 subjects with nicotine or cotinine on both scans, 13 subjects with caffeine on only 1 scan, 12 subjects with tobacco on only 1 scan, and 1 subject with caffeine on only 1 scan, but with cotinine on both scans. Serum caffeine levels were low, median 1.6 mg/l (IQR: 1.3 to 1.9 mg/l), as were tobacco tests for urine nicotine, median 14 ng/ml (IQR: 4 to 120 ng/ml), and cotinine, median 24 ng/ml (IQR: 4 to 182 ng/ml). Our results did not differ in any significant fashion after excluding the 21 pairs with detectable caffeine at either study.

In the 5 subjects with caffeine on only 1 scan who underwent repeat dipyridamole testing, stress flow was significantly reduced by caffeine (\( \Delta = 0.67; 95\% \) confidence interval 0.17 to 1.18 ml/min/g; \( p = 0.021 \)), and CFR demonstrated a downward trend (\( \Delta = 0.52; 95\% \) confidence interval 0.14 to 1.17; \( p = 0.09 \)). Only 3 subjects had tobacco on only 1 scan who underwent repeat dipyridamole testing, and differences for stress flow and CFR were not significant.

Of the 3 patients who had severe angina during vasodilation, 2 occurred with dipyridamole, but only 1 with regadenoson. Only 1 with dipyridamole, but only 1 with regadenoson had significant ST-segment depression during vasodilation, 5 occurred with dipyridamole, and only 1 with regadenoson (\( p = 0.22 \) by McNemar). No patient had severe angina or significant ST-segment depression with both vasodilators, even after excluding pairs with detected serum caffeine.

**DISCUSSION**

Our paired study comparing regadenoson to dipyridamole hyperemia for cardiac PET imaging demonstrated that regadenoson used per the package insert (15) achieved approximately 80% of absolute stress flow and CFR. As expected from basic pharmacological and physiological principles, the timing of radiotracer injection after the regadenoson bolus affected the degree of observed hyperemia. Activating the Rb-82 generator 55 s after beginning the regadenoson bolus improved the result to about 90% of dipyridamole hyperemia.

A large number of published reports supports the clinical utility of quantifying flow using cardiac PET, as we have summarized recently (16). Global CFR can stratify prognosis, quantifying the net effect of risk factors, microvascular disease, epicardial focal and diffuse atherosclerosis, and even noncoronary diseases such as aortic stenosis. For clinicians and researchers using cardiac PET, the inferior hyperemia provided by regadenoson blunts the benefits of quantifying absolute flow and CFR.

Clearly, the timing of the regadenoson bolus relative to radiotracer injection must influence the quantified stress flow and therefore CFR. Unlike intracoronary pressure and flow sensors that allow for continuous readings, nuclear imaging requires comparatively much longer acquisition periods in addition to the time for tracer circulation and uptake. During the development of regadenoson, data regarding bolus timing came from intracoronary flow sensors in animal models as well as a small number of humans. However, these surrogates for radiotracer kinetics and associated flow quantification provide a suboptimal guide for timing a radionuclide injection, given several factors not accounted for by instantaneous pressure and flow wire measurements (delay and dispersion by venous and lung transit and cardiac output; and time-dependent myocardial extraction).

Our much more extensive exploration of bolus timing suggests that the existing regadenoson package insert (15) should be revised because it provides only about 80% of dipyridamole hyperemia for cardiac PET. Instead of the current recommendation to “administer the radionuclide myocardial perfusion imaging agent 10–20 seconds after the saline flush” (15), our data favor a 50- to 60-s delay after...
the saline flush. The trend in Figure 2 could be extended and made more granular to identify the bolus timing (or timings, if a plateau period exists) associated with the highest average hyperemia. Because of the scintigraphic imaging technique and immeasurable individual patient factors like cardiac output and regadenoson pharmacodynamics, optimal bolus timing in nuclear cardiology can realistically only be a group average.

Despite giving explicit instructions before the PET scan and asking detailed questions at the time of each visit to exclude noncompliance, we still detected residual serum caffeine in 8% of cases and evidence of tobacco in 9%. Caffeine is well known to blunt hyperemia (7), although we did not see this effect in our small, paired subgroup. Discovering residual serum caffeine in 8% of cases in this study was smaller than 15% in a cohort of young, normal volunteers (7) and 19% in a clinical population (17). Together, these findings suggest that routine caffeine screening may be necessary in addition to patient instructions and questioning, especially when quantifying absolute flow.

Intriguingly, dipyridamole produced more severe angina (2 vs. 1) and significant ST-segment depression (5 vs. 1) than regadenoson, although these findings are limited by very small sample sizes. Further work could explore the suggested hypothesis that the longer duration and superior vasodilatory potency of dipyridamole compared with regadenoson more often provokes these diagnostically important clinical and electrocardiographic responses.

**COMPARISON TO EXISTING PUBLISHED REPORTS.** Regadenoson has been compared in humans to adenosine or dipyridamole in 4 general settings: PET imaging; single-photon emission computed tomography (SPECT) imaging; cardiac magnetic resonance imaging; and intracoronary FFR. Table 3 summarizes the existing literature across these categories compared with the current study, with an emphasis on important details like flow quantification, sample size, and paired versus unpaired designs (6,18–27). A few aspects deserve special comment.

No previous PET study has both quantified absolute flow and used a paired design. Relative uptake defects by PET using summed stress and difference scores found no difference between paired regadenoson and dipyridamole (18), but did not quantify flow. Absolute flow did not differ between unpaired cohorts that received regadenoson and dipyridamole (20). However, a paired design augments the ability to detect a difference between groups, likely explaining the discordance between their findings and ours.

A large study found no significant difference in SPECT defects using paired regadenoson and adenosine (21). Similar to our study, their clinical population was largely normal, with only 9% demonstrating a large reversible defect. Differing from our study, SPECT did not quantify absolute flow or employ attenuation correction, and it has an inherently lower spatial resolution than PET. Therefore, these results are likely consistent with our observation of a reduction in absolute stress flow and CFR.

A prior cardiac magnetic resonance study compared absolute flow among regadenoson, dipyridamole, and adenosine, with 15 normal volunteers receiving all 3 vasodilators (22). Interestingly, they also used a longer delay between the regadenoson bolus and tracer injection of 70 s, similar to our findings in Figure 2, but without explanation or systematic exploration of the effect of bolus timing. However, unlike our results, they found that regadenoson provided superior stress flow compared with dipyridamole or adenosine (3.58 ± 0.58 ml/min/g vs. 2.81 ± 0.67 ml/min/g and 2.78 ± 0.61 ml/min/g, respectively) with similar ordering for CFR (3.11 ± 0.62 vs. 2.61 ± 0.57 and 2.7 ± 0.30, respectively). Several potential explanations exist, notably the much smaller sample size and different imaging modality compared with our cohort.

**TABLE 3** Review of Existing Published Reports

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>Comparison</th>
<th>Paired?</th>
<th>Flow?</th>
<th>N</th>
<th>Summary</th>
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<tr>
<td>PET</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cullom et al. (18)</td>
<td>Dipyridamole</td>
<td>Yes</td>
<td>No</td>
<td>32</td>
<td>No flow, same uptake</td>
</tr>
<tr>
<td>Bravo et al. (19)</td>
<td>Dipyridamole</td>
<td>No</td>
<td>Yes</td>
<td>57</td>
<td>Same flow</td>
</tr>
<tr>
<td>Goudarzi et al. (20)</td>
<td>Dipyridamole</td>
<td>No</td>
<td>Yes</td>
<td>104</td>
<td>Same flow</td>
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<tr>
<td>Current study</td>
<td>Dipyridamole</td>
<td>Yes</td>
<td>Yes</td>
<td>126</td>
<td>Inferior flow</td>
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<td>SPECT</td>
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<td>Hendel et al. (6)</td>
<td>Adenosine</td>
<td>Yes</td>
<td>No</td>
<td>36</td>
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<td>Iskandrian et al. (21)</td>
<td>Adenosine</td>
<td>Yes</td>
<td>No</td>
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<td>CMR</td>
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<td>Vasu et al. (22)</td>
<td>Both</td>
<td>Yes</td>
<td>Yes</td>
<td>15</td>
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<td>DelBella et al. (23)</td>
<td>Adenosine</td>
<td>Yes</td>
<td>Semi</td>
<td>28</td>
<td>Same flow</td>
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<td>FFR</td>
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<tr>
<td>Arumugham et al. (24)</td>
<td>Adenosine</td>
<td>Yes</td>
<td>No</td>
<td>20</td>
<td>Δ = 0.004 ± 0.025</td>
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<td>Nair et al. (25)</td>
<td>Adenosine</td>
<td>Yes</td>
<td>No</td>
<td>25</td>
<td>Δ = 0.003 ± 0.016</td>
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<tr>
<td>Prasad et al. (26)</td>
<td>Adenosine</td>
<td>Yes</td>
<td>No</td>
<td>57</td>
<td>Δ = 0.002 ± 0.025</td>
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<tr>
<td>van Nunen et al. (27)</td>
<td>Adenosine</td>
<td>Yes</td>
<td>No</td>
<td>100</td>
<td>Δ = &lt;0.01 ± 0.01</td>
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</table>

**Legend:** CMR = cardiac magnetic resonance; FFR = fractional flow reserve; PET = positron emission tomography; Semi = semiquantitative; SPECT = single-photon emission computed tomography.
a standard deviation similar to repeat FFR measurements using the same vasodilator. Therefore, instantaneous hyperemia after regadenoson bolus appears to reach the same peak level as during adenosine infusion. However, the duration of the hyperemic plateau demonstrates great heterogeneity among individuals: 14% < 30 s, 26% < 60 s, and 65% < 3 min (27). The variation in hyperemic duration from the instantaneous FFR data supports our observed group reduction in absolute stress flow and CFR, especially when accounting for added heterogeneity of radiotracer transit times from intravenous injection until reaching the coronary arteries and time-dependent myocardial uptake of radionuclide.

**STUDY LIMITATIONS.** Our design did not blind the physician, patient, or nuclear medicine technologist to the vasodilator, or use a blinded core lab. However, we randomized the order of regadenoson and dipyridamole and used standard, objective, approved software packages for image processing and quantitative analysis, including flow measurements. We employed the recommended 10 s injection of regadenoson. Future studies could explore hemodynamic and flow responses when altering this duration.

Dipyridamole served as our reference vasodilator instead of adenosine, reflecting our own clinical practice and likely a majority of other cardiac PET centers. The equivalence between the 2 agents for cardiac PET has been explored in several previous studies, mainly showing similar hyperemia. Therefore, we surmise that results would also hold when comparing regadenoson to adenosine.

Our cohort included few patients with moderate or large defects. We suspect, but can only hypothesize, that relative uptake equivalence may not hold for this subset. Indeed, our results indicate that flow quantification enables detection of significant effects with a smaller sample size that relative uptake images—a point worth emphasizing for phase 1 and 2 and diagnostic accuracy trials. Finally, we did not explore whether the clinical decisions resulting from regadenoson versus dipyridamole would lead to significantly different long-term patient outcomes because of the low risk, predominantly normal or only mild relative uptake defects in our study population.

**CONCLUSIONS**

When administered per the standard timing protocol of the package insert (15), regadenoson achieved only 80% of dipyridamole hyperemia quantitatively imaged by cardiac PET with Rb-82. Delaying radionuclide injection further after the regadenoson bolus improved its hyperemia to around 90% of dipyridamole levels.

**REFERENCES**


In quantitative myocardial perfusion due to arterial input selection. J Am Coll Cardiol Img 2013;6:559-68.


