A useful and easy to develop combined stress test for myocardial perfusion imaging: Regadenoson and isometric exercise, preliminary results

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Background. **Regadenoson, a selective A2a receptor agonist, is a vasodilator increasingly used in myocardial perfusion imaging. Adjunction of isometric exercise is a simple method that could improve side effect profile while providing better image quality.**

Methods. **Patients undergoing SPECT MPI were prospectively enrolled in handgrip-Regadenoson (HG-Reg test, N = 20) and Regadenoson (Reg) stress test (N = 40). Investigator blinded to stress test analyzed clinical data and images.**

Results. **Heart rate (HR) increase was statistically higher in the HG-Reg group (27 vs 22 bpm, $P = .019$). Decrease in SBP was less frequent in the HG-Reg group than in the Reg group (55% vs 85.5%, $P = .005$), there were less drops >10 mmHg (45% vs 77.7%, $P = .012$). During stress testing, fewer subjects reported at least one side effect in the HG-Reg compared to Reg group (70% vs 92.5%, $P = .021$). Images were more often classified as good in the HG-Reg group (75% vs 52.5% in the Reg group, $P = .25$).**

Conclusions. **Adjunction of handgrip exercise to Regadenoson administration is a well-tolerated and easy method, without loss of time. Furthermore, image quality seems to be better. (J Nucl Cardiol 2017;24:34–40.)**

Key Words: Exercise stress • vasodilator stress • myocardial perfusion imaging • Regadenoson

Abbreviations			
SPECT MPI	Single-photon emission computed tomography myocardial perfusion imaging	ECG	Electrocardiogram
		QGS/QPS	Quantitative gated SPECT/Quantitative perfusion SPECT
		CAD	Coronary artery disease
HG	Handgrip	THR	Target heart rate
HR	Heart rate		
SBP	Systolic blood pressure		

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INTRODUCTION

Regadenoson has been increasingly used in patients unable to perform an adequate effort for the past few years in

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myocardial perfusion imaging (MPI). Its diagnostic performances have been compared with other pharmacological agents and are equivalent to adenosine and dipyridamole, with less side effects.[1] Regadenoson has the advantage of being a selective A2a receptor agonist, allowing its use in chronic obstructive pulmonary disease and asthma patients with a fixed dose (no adapted dose for renal or hepatic failure) and a bolus administration over 10 seconds, with a rapid onset of action. Exercise stress test or test combining exercise and pharmacological hyperemia are preferred over pharmacological test because it improves patient tolerance and image quality.[2] Symptom-limited test allows exercise information while optimizing myocardial SPECT results.[3] Studies with symptom-limited strategies have been conducted with Regadenoson.[4,5] Those studies showed the safety and efficacy of the method, in spite of being off-label. Such protocols that consist in a combined Regadenoson test with maximal exercise carry the risk of inducing ''double stress'' in case of positive ischemic exercise stress test. Several methods have been studied,[6] combining Regadenoson with low-level exercise,[7-9] or with Regadenoson at peak exercise only when submaximal heart rate response is reached.[10-14] They have shown to be feasible, with no increase in adverse events and with more favorable hemodynamic response and less use of aminophylline than with Regadenoson only.[8] It would be preferable to administer Regadenoson during recovery rather than at peak exercise because some patients had significant changes in systolic blood pressure (SBP), with also a greater safety margin.[11] However, these methods will prolong time of procedures. Our study aimed at evaluate whether the addition of a handgrip stress test in Regadenoson procedure was safe, feasible, and able to improve image quality.

METHODS

Study Design

We prospectively compared 40 consecutive patients undergoing a routine Regadenoson test (Reg) to 20 consecutive patients with a combined handgrip-Regadenoson test (HG-Reg) conducted in the Nuclear Cardiology Laboratory at Bordeaux Hospital (Bordeaux, France).

Participants and Setting

Patients referred for stress MPI were consecutively included, from November 2014 to February 2015. Patients were excluded if they had uncontrolled hypertension, known hypertrophic cardiomyopathy, severe symptomatic aortic stenosis, decompensated heart failure, greater than first-degree atrioventricular conduction block, active bronchospasm, or acute coronary syndrome within 1 week and had used methylxanthines within 12 hours prior to testing. All subjects provided informed consent prior to stress testing. All subjects underwent a history and physical examination on arrival in the stress-testing area.

Regadenoson protocol (Reg)

Supine patients received at rest an injection of Regadenoson (0.4 mg intravenous bolus over 10 seconds followed by saline flush; Rapidscan Pharma Solutions EU Ltd. London, United Kingdom); Radiotracer was injected 30 seconds after Regadenoson. All subjects were monitored for at least 5 minutes following stress testing, with 12-lead ECG every minute. Symptoms, adverse effects, blood pressure, and heart rate measurements were collected during each stage of the protocol (2 minutes before the injection; at injection; and every 1 minutes for at least 5 minutes during recovery) until symptoms, significant hemodynamic, or ECG changes had resolved.

Handgrip-Regadenoson Protocol (HG-Reg)

Patients started handgrip 2 minutes before Regadenoson injection and continued until the end of the pharmacological test monitoring (5-7 minutes after injection). Same protocol was used for the injection of the Regadenoson and monitoring.

MPI and Interpretation

Single-photon emission computed tomography myocardial perfusion acquisition and image processing were performed in accordance with European Association of Nuclear Medicine Society of Nuclear Cardiology guidelines.[15] All images analyzed in this study were part of a routine rest-stress protocol using 99mTc-tetrofosmin. The injected isotope dose was 296-809 MBq, depending on patient's weight. Images were acquired with the patient prone starting 20 minutes after rest injection (2.5 MBq/kg) and 10 minutes after stress injection (8 MBq/kg) using a Cadmium-Zinc-Telluride camera (Discovery NM 530c; GE Healthcare). The imaging times were 10 and 5 minutes, respectively. Acquisitions were preceded by automatic heart positioning in the optimal area, or ''quality field of view,'' using real-time persistence imaging. All acquisitions were electrocardiography-gated, and the cardiac cycle was divided into 16 equal intervals. Maximum-penalized-likelihood iterative reconstruction was performed on all gates using a dedicated iterative algorithm with integrated collimator geometry modeling. A Butterworth post-processing filter (frequency, 0.37; order, 7) was applied to the reconstructed axial slices, which were subsequently reformatted in the standard cardiac axis for analysis (short axis, vertical long axis, and horizontal long axis). Images were analyzed with a commercially available software package (QPS/QGS; Cedars-Sinai Medical Center). Automatic processing was performed in all cases, with the option of manual correction in cases of inadequate anatomic delineation. All images were interpreted by consensus read of 2 investigators blinded to stress test protocol and results. Overall perfusion and gated image quality were described as poor (if late images were

needed or if an extra-myocardial uptake induced artifact) or good (no myocardial artifact on first images).

Statistical Analysis

Baseline characteristics were analyzed as percentages or means ± standard deviations. Continuous variables were compared using the Student *t* test or non-parametric Mann–Whitney test if the characteristics were not normally distributed, and categorical variables were compared with a fisher test. Side effects were reported as percentages. All analyses were conducted with NCSS (Dawson edition; Kaysville, UT).

RESULTS

Population

Between November 2014 and February 2015, research staff screened a total sample of 60 patients referred for stress MPI. No patients were excluded. The mean age was 70 years and 28% were female, the two groups were similar regarding these parameters. Evaluation of stable coronary artery disease (CAD) was the most common indication for stress MPI. Population's characteristics and clinical data are summarized in Table 1.

Hemodynamic Changes

Heart rate (HR) increase was statistically higher in the HG-Reg group (27 vs 22 bpm, $P = .019$). Maximum HR and percentage of age-predicted maximum HR were higher in HG-Reg group (99 vs 92, $P = .88$ and 66% vs 61%, $P = .108$, respectively). In this group 40% of patients had an increase of 30 bpm at least vs 13%, respectively, ($P = .099$) and 10% of patients achieved 85% target heart rate (THR) calculated as 220-age (years), vs 3% in the Reg group (not statistically significant). Mean resting SBP were similar in the two groups. Decrease in SBP was markedly less frequent in the HG-Reg group than in the Reg group (55% vs 85.5%, $P = .005$), there were less drops >30 mmHg in the HG-reg group (10% vs 22.5%, $P = .238$), as well as drops >10 mmHg (45% vs 77.7%, $P = .012$). Mean minimum SBP when decreased and maximum SBP when increased during stress test seems less marked in the HG-Reg group, but these results were not statistically significant.

Increase in systolic blood pressure (SBP) was less frequent than decrease in the two groups and occurred in 45% of patients in the HG-Reg group and 12.5% in the Reg group, with similar mean values, 22 and 19 mmHg, respectively. The greatest individual drop in SBP was 75 mmHg in the HG-Reg group and 50 mmHg in the Reg group (blood pressure were 160 and 195 mmHg prior to stress test, respectively) and the greatest increase in SBP observed was 40 mmHg in the HG-Reg group (from 100 mmHg prior to stress test). In one patient in the HG-Reg group, SBP increased up to 235 mmHg, who had an anxiety exacerbation prior to drug administration. Blood pressure in all HG-Reg subjects returned to baseline without specific intervention. Hemodynamic parameters are listed in Table 2.

Table 1. Patient demographics and clinical data

Variable	Total (N = 60)	HG-Reg (N = 20)	Reg (N = 40)	*P* value
Female	17 (28%)	7 (35%)	10 (25%)	.418
Age (years)	70 ± 13	70 ± 11	70 ± 14	.086
BMI (kg/m^2), mean ± SD	28 ± 6	27 ± 6	28 ± 6	.327
Known coronary artery disease	39 (65%)	11 (55%)	28 (70%)	.251
Indication for pharmacological test				
Left bundle branch block	7 (12%)	2 (10%)	5 (12.5%)	.776
Pacemaker	6 (10%)	1 (5%)	5 (12.5%)	.361
Limited physical capacity	30 (50%)	11 (55%)	19 (47.5%)	.584
Exercise test adverse event	3 (5%)	0	3 (7.5%)	.209
Hypertension	1 (2%)	0	1 (2.5%)	.476
Surgical abdominal aneurism	2 (3%)	2 (10%)	0	.042*
Arteritis	12 (20%)	3 (15%)	9 (22.5%)	.494
Wolff-Parkinson-White syndrome	1 (2%)	1 (5%)	0	.154

Numeric data are given as mean ± standard deviation (SD)
BMI, body mass index
P values are between HG-Reg and Reg groups (*statistically significant, P< 0.05)

Table 2. Hemodynamic changes

Variable	HG-Reg (N = 20)	Reg (N = 40)	*P* value
Resting HR (bpm)	70 ± 16	70 ± 12	.880
HR increase (bpm)	27 ± 9	22 ± 15	.019*
Number of patients with HR rate increase >30 bpm	8 (40%)	8 (13%)	.099
Maximal HR	99 ± 19	92 ± 20	.209
Percentage of age-predicted maximum HR achieved (220-age in years)	66 ± 13	61 ± 11	.108
Number of patients achieving 85% THR	2 (10%)	2 (3%)	.464
Resting SBP (mmHg)	145 ± 25	143 ± 25	.052
SBP variation during stress	29 ± 26	20 ± 11	.204
Minimum SBP, when decreased during stress test (mmHg)	129 ± 30	122 ± 22	.559
Decrease (mmHg)	27 ± 23	20 ± 11	.668
Number of decrease in SBP	11 (55%)	35 (85.5%)	.005*
Number of drop >30 mmHg	2 (10%)	9 (22.5%)	.238
Number of drop >10 mmHg	9 (45%)	31 (77.5%)	.012*
Maximum SBP, when increased during stress test (mmHg)	167 ± 35	171 ± 15	.012*
Increase (mmHg)	30 ± 28	19 ± 14	.360
Number of increase in SBP	9 (45%)	5 (12.5%)	.005*

Numeric data are given as mean ± standard deviation (SD)
Bpm, beat per minute; *HR*, heart rate; *SBP*, systolic blood pressure
P values are between HG-Reg and Reg groups (*statistically significant, $P < 0.05$)

Side Effects and Protocol Development

Total test time, including administration of pharmaceutical agent, handgrip exercise, injection of radiotracer, and recovery time with continuous electrocardiographic monitoring, was slightly increased in the HG-Reg group (9 ± 2 vs 8 ± 2 minutes, $P = .005$).

Side effects are reported in Table 3. During stress testing, fewer subjects reported at least one side effect associated with HG-Reg in comparison to Reg subjects (70% vs 92.5%, $P = .021$). However, mean number of side effects was not statistically different in the two groups ($P = .090$). Chest discomfort was the most common side effect in both groups but without significative difference. Nausea was the only side effect with statistical difference and appears more common with the HG-Reg than with Reg ($P = .038$). There were left bundle branch block in two patients and one chest pain requiring trinitrine in one patient of the Reg-group, and none in the HG-Reg group. Aminophylline was used in only one patient of the HG-Reg group. One patient in the Reg group presented a bradycardia under 40 bpm rapidly resolving.

No patient shows severe adverse event and none declare ischemic symptoms or ECG changes that would have need urgent coronary angiography.

MPI Analysis

Representative patients with image quality classified as poor are shown in Figure 1. There were more images classified as good in the HG-Reg group than in the Reg group, as shown in Figure 2. This difference was not statistically significant (75% vs 52.5%, $P = .25$).

DISCUSSION

Our method aimed at determining if addition of handgrip to administration of Regadenoson was safe and improved image quality. The advantages are that most of patients are able to achieve this exercise, the procedure is easy to develop in a stress-testing laboratory and is not contraindicated by usual contraindications to exercise test. It could probably be used in left bundle branch block since only a slight increase in heart rate has been observed but larger studies are needed. The adjunction of handgrip test prolonged only slightly the test duration in our study. This simple method does not carry as much prognostic information as a symptom-limited exercise, however it has been used for detection of CAD.[16] Our strategy will not reduce use of vasodilator as strategies already published.[4,5] It has the advantages to not induce a double stress that may expose to an extra risk, not

Table 3. Side effects

Variable	HG-Reg (N = 20)	Reg (N = 40)	*P* value
Total test time (minutes)	9 ± 2	8 ± 2	.005*
Recovery time (minutes)	7 ± 2	6 ± 2	.005*
Side effects	1.7 ± 1.4	1.1 ± 1.0	.090
Patients reporting at least one side effect	14 (70%)	37 (92.5%)	.021*
Number of patient's side effect	2.4 ± 0.9	1.6 ± 0.8	.006*
Chest discomfort	9 (45%)	16 (40%)	.711
Headache	4 (20%)	5 (12.5%)	.443
Nausea	4 (20%)	1 (2.5%)	.021*
Chest pain	2 (10%)	2 (5%)	.464
Dizziness	3 (15%)	3 (7.5%)	.361
Arrhythmias	3 (15%)	7 (17.5%)	.810
Abdominal discomfort	2 (10%)	5 (12.5%)	.776
Throat tightness	2 (10%)	-	.042*
Flushing	2 (10%)	3 (7.5%)	.741
Palpitations	2 (10%)	-	.042*
SBP <90 mmHg	1 (5%)	-	.154
Dyspnea	1 (5%)	3 (5%)	.714
Use of aminophylline	1 (5%)	-	.154
Neck pain	1 (5%)	-	.154
Bradycardia <40 bpm	-	1 (2.5%)	.476
Left bundle branch block	-	2 (5%)	.309
Chest pain requiring sublingual trinitrine	-	1 (2.5%)	.476
ST depression	-	1 (2.5%)	.476

Numeric data are given as mean ± standard deviation (SD)
SBP, systolic blood pressure
P values are between HG-Reg and Reg groups (*statistically significant, $P < .05$)

completely understood, opposed to a peak exercise or during and after recovery protocols.[6]

In our study, the HG-Reg method was statistically associated with less subjects reporting at least one side effect than with Regadenoson alone (70% vs 92.5%, $P = .021$).

The HG-Reg group had better hemodynamic profile changes. We found higher heart rates increase in HG-Reg group than in the Reg group, with higher maximal heart rates. This could lead to depict more ischemic areas as shown with dipyridamole.[17] As it could be expected, there were more patients increasing SBP in the HG-Reg group. Although larger variations in SBP in the HG-Reg group, there were less drops over 30 and 10 mmHg. It has to be emphasizing since a recent alert in risk of seizures and strokes mediated by hemodynamic changes induced by Regadenoson has recently been issued in France. With dipyridamole, the addition of the isometric stress test results in a significant decline in hyperemic response induced by standard-dose, that may be due to increased extravascular resistive forces or an increase in a mediated coronary vasoconstriction associated with exercise.[18] If exercise in addition to pharmacologic stress significantly decreases hyperemic myocardial blood flow and flow reserve, diagnostic performances seem unchanged as proved by many studies encouraging mixed protocols.

Image quality has been markedly better in the HG-Reg group in our study, as previously observed with combined Regadenoson and exercise protocols.[9-13] A study showed that use of handgrip was safe, feasible, and efficient with Dobutamine stress echocardiography and may lead to improve diagnostic performances. Isometric handgrip test is known as a simple method for detection of coronary artery disease (CAD), but is limited by its low sensitivity. Combined with other method it may improve diagnostic performances, as already proved for dipyridamole.[2] Indeed, a study showed that longitudinal speckle-tracking strain combined with handgrip may be useful for diagnosis of

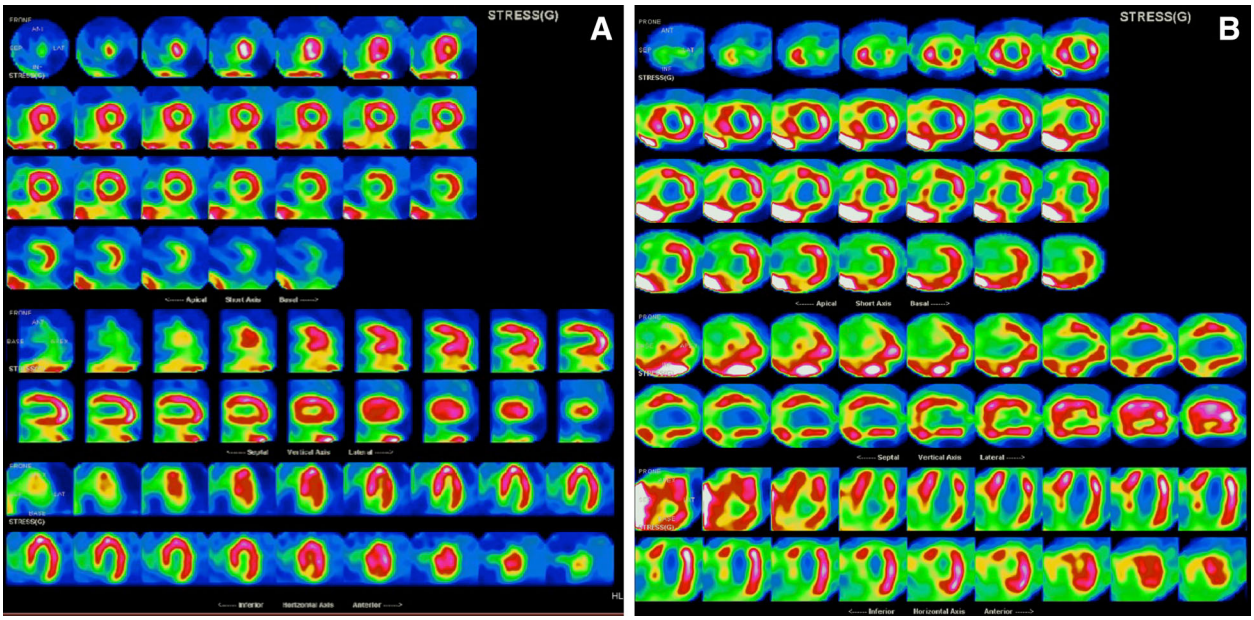

Figure 1. Examples of 99mTc-tetrofosmin myocardial perfusion imaging (left ventricular tomograms in short axis, horizontal, and vertical long axis) stress image quality evaluated as poor in a patient presenting an extra-myocardial uptake with a minimal artifact (**A**), and an intense sub diaphragmatic uptake, requiring repeat imaging to allow for interpretation (**B**).

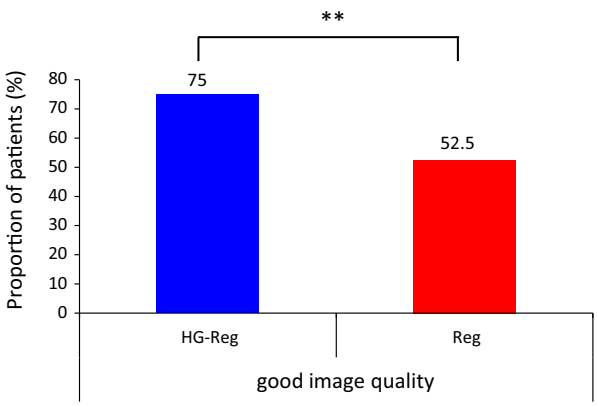

Figure 2. Image quality proportion in HG-Reg (blue) and Reg (red). Data are from the 20 patients and 40 patients respectively. They are presented as percentages. *P* value is for difference between the two groups (Chi-squared test).

ischemic myocardial segments.[19] Therefore the handgrip protocol combined with Regadenoson may improve MPI sensitivity in detecting CAD. Further works are already being conducted in larger populations in order to confirm that side effects profile is favorable, image quality is improved and to determine whether diagnostic certainty is impacted.

However, our study presents limitations. First, the main limitation is the small population of our study in these preliminary results. Another limitation is the rhythm and intensity of the isometric exercise that cannot be objectively controlled.

NEW KNOWLEDGE GAINED

Isometric exercise is feasible with regadenoson test and can lead to better diagnosis information, without increasing side effects.

CONCLUSION

Adjunction of an isometric exercise to Regadenoson stress test is easy to implement in laboratories and seems to carry advantages in comparison to symptom-limited exercise. Hemodynamic profile and image quality tend

to be improved and fewer side effects had been observed. Improved image quality must be comforted by larger studies dealing with handgrip exercise combined with Regadenoson.

Disclosure

The authors have no conflict of interest to disclose.

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