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Combination of physical exercise and adenosine improves accuracy of automatic calculation of stress LVEF in gated SPECT using QGS software

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Abstract:

BACKGROUND: Combining exercise and adenosine during the stress phase of myocardial perfusion imaging (MPI) is known to reduce adverse effects and improve image quality. The aim of this study was to assess whether it can also improve the automatic calculation of left ventricular ejection fraction (LVEF) by QGS software package, during the stress phase of Gated SPECT.

MATERIAL AND METHODS: One hundred patients who had stress Gated SPECT were retrospectively included in this study. Gated data of those who had adenosine only (50 patients = group A) was compared with those obtained in another group of 50 patients who had added bicycle exercise (Group B). All had identical image acquisition protocol using ^{99m}Tc-tetrofosmine. Clinical adverse effects, changes in blood pressure (BP), heart rate (HR), and ECG were monitored. Visual assessment of sub-diaphragmatic uptake and accuracy of automatic regions of interest (ROI's) drawn by the software were noted. Regions of interest that involved sub-diaphragmatic uptake and resulting in low LVEF were manually adjusted to include the left ventricle only, and the frequency of manual adjustment was noted.

RESULTS: No significant difference was noted in age, sex, baseline BP and HR between groups A and B. Adverse effects occurred less often in group B compared to group A (12% *vs.* 24%, p = 0.118). Maximum HR and BP achieved during stress were significantly higher in group B compared to group A (p = 0.025, p = 0.001 respectively). The number of patients who had faulty ROI's and low LVEF, who needed manual adjustment of ROI's, were higher in group A compared to group B (16% *vs.* 6%, p = 0.025). The values of LVEF showed significant improvement following manual adjustment of ROI's, increasing from a mean of 19.63 ± 15.96 to 62.13 ± 7.55 (p = 0.0001) and from 17.33 ± 9.5 to 49.67 ± 7.7 (p = 0.0014) in groups A and B respectively.

CONCLUSION: The addition of exercise to adenosine significantly improves the automatic calculation of LVEF by QGS software during Gated SPECT and reduces the need for manual adjustment.

Keywords: gated SPECT, adenosine, physical exercise, sub-diaphragmatic uptake, LVEF

Introduction

Stress-rest myocardial perfusion imaging (MPI) is recommended as an initial noninvasive method for the evaluation of known or suspected coronary artery disease (CAD) [1]. The increasingly used ECG-Gating during tomographic acquisition (Gated SPECT) provides additional information regarding myocardial function such as the assessment of wall motion, thickening and estimation of LVEF.

The stress phase of MPI is commonly achieved by pharmacological agents such as vasodilators and inotropic agents and rarely by physical exercise alone due to logistic reasons. In the United Kingdom, the common trend is to use adenosine due to its safety and

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short half-life, switching to dobutamine when there are contraindications to the former such as chronic obstructive airway disease.

Infusing a vasodilator such as adenosine will reduce coronary vascular resistance and increase coronary blood flow, thus creating a differential flow that will highlight areas of reduced perfusion. However, it can induce adverse effects (hypotension, A-V conduction problems) and increases splanchnic blood flow. The latter will lead to unwanted sub-diaphragmatic concentration of perfusion radiopharmaceuticals and reduce the count rate in the inferior wall with deleterious effect on image quality and interpretation.

Adding low-level exercise to adenosine during stress MPI can reduce adverse effects and improve image quality [2–6]. However, the value of added exercise in Gated SPECT has not yet been assessed.

With the increasing use of Gated SPECT, functional data such as the LVEF has become part of the assessment of CAD. Most centers rely on commercial software to calculate LVEF through automatic selection of regions of interest around the myocardial wall in end systole and end diastole. Variability in automatic calculations has been attributed to injected dose, time of imaging, extra-cardiac activity, heart size, pixel size and reconstruction parameters [7–9].

The aim of this study was to investigate whether combining adenosine with low-level exercise would enhance the calculation of LVEF by improving the automatic selection of ROI's, and thereby reducing the frequency of manual adjustment which can be time consuming in a busy department.

Table 1. Baseline characteristics in groups A and B

	Group A (n = 50)	Group B (n = 50)	P value
Age (y)	65.28 ± 10.3	62.44 ± 11.4	NS
Males	20	26	NS
Females	30	24	NS
Resting heart rate [beats/min]	69.93	70.5	NS
Resting systolic blood pressure [mm Hg]	140.2 ± 25.3	138.0 ± 26.2	NS
Resting diastolic blood pressure [mm Hg]	74.2 ± 10.6	77.18 ± 18	NS

NS — non significant

Materials and methods

Patients selection

Retrospectively, using archives of patients referred for Gated SPECT between September 2004 and February 2005, we sequentially selected 50 patients who underwent adenosine infusion only (Group A), and 50 patients who had a combination of adenosine and low-level bicycle exercise (Group B). They included 46 males and 54 females (age range of 56–79 years, mean: 63.86 (Table 1).

Stress protocol

Caffeine was discontinued for 24 hours prior to stress and verbal consent was obtained from all patients. Those in group A underwent a 6-minute intravenous adenosine infusion of 140 μg/ /kg/min without exercise because of physical inability. The procedure was carried out under constant monitoring of blood pressure (BP), heart rate (HR) and 12-lead ECG. Patients in group B had additional low-level (average 15 W) bicycle exercise while in a semi-reclining position for the entire 6 minutes of stress.

Four minutes into stress, 400 MBq 99mTc-tetrofosmine was injected intravenously, and patients in both groups continued the stress protocol for another two minutes.

Adverse effects and symptoms were recorded and stress was stopped if HR or ECG changes exceeded the recommended guidelines [10]. Monitoring of BP, HR and ECG was continued until return to pre-stress levels. Hypotension was defined as a drop of > 30 mm Hg in systolic blood pressure.

Imaging protocol

The patients were asked to eat and drink (typically a Chocolate bar and hot drink) after stress to reduce counts originating from non-cardiac sub-diaphragmatic sources. Image acquisition was performed after 45 minutes with a dual-detector gamma camera (ECAM, Siemens Medical Systems Inc. IL, USA) equipped with low-energy, high-resolution collimators. Sixty-four views were acquired over 180° using a 'step and shoot' protocol and 30 seconds per view. A 64 $\times$ 64 matrix was used with a zoom of 1.45 giving a pixel size 6.59 mm. A fixed ECG gating widow was used to gate the projections into 8 frames.

The acquired data were reconstructed with Hermes software (Nuclear Diagnostics, Stockholm, Sweden) by filtered back projection with a butterworth filter (order 5, frequency cutoff 0.5 cycles/cm).

Calculation of LVEF

Left ventricular ejection fraction was calculated for both groups using Quantitative Gated SPECT (QGS, Cedars-Sinai Medical Center, Los Angeles, Calif., USA) software package. By default, the software automatically draws left ventricular ROI's and calculates the LVEF. For the purpose of this paper, the lower limit of LVEF was considered as 50%.

Visual assessment of non-cardiac sub-diaphragmatic uptake, accuracy of the drawn ROI's (demonstrating the entire left ventricle) and values of LVEF were checked for all patients.

Whenever ROI's had included parts of sub-diaphragmatic areas (faulty ROI's), they were manually adjusted to include the boundary of the left ventricle only, and processed to derive new values of LVEF that were compared with the old values. The frequency of manual adjustment of ROI's was compared between groups A and B.

Statistical analysis

Data are reported as either mean ± standard deviation or frequency. Comparisons were made by independent T-test between group means and by paired T-test within a group.

A p value < 0.05 was considered as statistically significant.

Results

Baseline data

No significant difference was noted in age and sex distribution between patients in groups A and B (Table 1). Likewise, there were no significant differences between mean baseline HR, systolic BP and diastolic BP between the two groups (70, 140 and 74 in group A compared to 70.5, 138 and 77 in group B

Table 2. Haemodynamic responses and ECG changes in groups A and B

	Group A (n = 50)	Group B (n = 50)	p value
Maximum heart rate [beats/min]	85.6 ± 18.3	93.7 ± 17.5	0.025
Highest systolic blood pressure [mm Hg]	130.1 ± 32.6	152.4 ± 28.0	0.001
Highest diastolic blood pressure [mm Hg]	67.40± 9.8	76.34± 16.5	0.006
ECG changes (%)	20	12	NS

NS — non significant

Table 3. Adverse reactions in groups A and B

	Group A (n = 50)	Group B (n = 50)
Hypotension	12	6
AV block	2	–
Chest pain	8	3
Dizziness	2	1
Total adverse reactions	12	6
Percentage of adverse reactions	24%	12%*

* p = 0.118

respectively).

Haemodynamic responses and adverse reactions

All patients managed to finish the 6-minute protocol without interruption, and none had serious or life-threatening adverse effects. Haemodynamic responses of both groups are shown in Table 2.

Mean peak HR, systolic and diastolic BP were higher in group B compared to group A (93.7 ± 17.5, 152.4 ± 28 and 76.34 ± 16.5 *vs.* 85.6 ± 18.3, 130.1 ± 32.6 and 67.4 ± 9.8 respectively) with a significant difference between the 2 groups (p = 0.025, p = 0.001 and p = 0.006 respectively). The frequency of non life-threatening adverse effects including hypotension, AV block, reversible chest pain, dyspnoea, and dizziness was less in group B compared to group A (12% *vs.* 24%, p = 0.118) (Table 3). 12 patients in group A developed hypotension compared to 6 in group B. the frequency and distribution of other adverse effects between the two groups are shown in Table 3.

Sub-diaphragmatic uptake and LVEF

Visual assessment showed 11 patients to have clear sub-diaphragmatic uptake. There was significantly higher frequency of sub-diaphragmatic uptake in group A compared to group B (16% *vs.* 6%, p = 0.025). All 11 patients with such uptake had faulty ROI's that included part or all of the sub-diaphragmatic region, and subsequently abnormally low LVEF ranging from 1–45% (mean 19.03% ± 15.96%) and 8–27% (mean 17.33% ± 9.5%) in groups A and B respectively.

Following manual adjustment of ROI's, the values of LVEF increased significantly in group A to a range of 50–75% (mean 62.13% ± 7.55%, p= 0.0001), and in group B to a range of 42––57% (mean 49.67% ± 7.5%, p = 0.0014).

Discussion

Coronary artery disease (CAD) remains a prominent cause of morbidity and mortality that drains a large proportion of health budget worldwide. Amongst the different imaging modalities, MPI is now established as a robust [11] and cost-effective [12–13] technique that is increasingly used in the diagnosis, prognostication and selection for revascularisation in patients with CAD [14]. This position was recently affirmed by the National Institute of Clinical Excellence (NICE) in the UK [15]. Gated SPECT improves the overall diagnostic value of MPI by providing information about wall motion, thickening and global LVEF.

The current trend in the UK is towards the increasing use of Gated SPECT with analysis of data by one of a handful of available commercial software that have been validated against first pass radionuclide angiography, echocardiography and MRI [7–8, 16–18]. Generally, these software use automatic algorithms to draw ROI's around the left ventricle in end systole and end diastole to calculate LVEF. Automatic selection of ROI's is an advantage that could save time and improve accuracy compared to manual selection.

Quantative Gated SPECT is by far the most commonly used software and its automatic calculation of LVEF was found to be reproducible and concordant with manual methods [18–19].

There are however some drawbacks to the use of these software. Hambye and colleagues have found variability in LVEF caused by differences in algorithms, pixel size and reconstruction parameters in different versions of the most commonly used packages [9], while Vallejo and colleagues, using a canine model, found that QGS is affected by background activity, injected dose and time of imaging [7–8].

We have observed that, in the majority of cases, the software would automatically and accurately draw ROI's around the LV. However, in the presence of extra cardiac uptake, automatic selection becomes faulty and requires manual adjustment, which may increase the workload in a busy department.

Our aim was to investigate if the need for manual adjustment of ROI's could be improved by the addition to exercise to adenosine.

Adenosine is now the most widely used pharmacologic stress agent in the UK. It causes coronary vasodilatation by binding to the A2a receptor, but peripheral vasodilatation is also mediated via the A2b receptor. The typical haemodynamic response to adenosine is a mild increase in heart rate, probably mediated by reflex response to peripheral vasodilatation, and a modest fall in systolic and diastolic blood pressure. Adenosine also stimulates A1 receptors causing atrio-ventricular conduction delay [20], which is considered an adverse effect that may lead to termination of stress.

The addition of low-level exercise to adenosine increases skeletal muscle workload and reverses the negative inotropic and chronotropic effects of adenosine and can reduce adverse effects and improve image quality in MPI. This was noted by Pennell and colleagues using ^{201}Tl as a perfusion agent [2]. Similar findings were reported with the use of ^{99m}Tc-sestamibi [5–6]. So far, there has been no data on the effect of added exercise in improving the value of gated data, particularly in improving the automatic calculation of LVEF.

Our results confirmed the reported increased efficiency of adenosine stress by adding low-level exercise. The peak HR, diastolic and systolic BP significantly increased compared to baseline values in group B compared to group A. These effects were unrelated to age or gender. We also report higher incidence of adverse effect attributed to adenosine infusion in group A compared to adenosine and exercise in group B (12% *vs.* 24%, $p = 0.118$).

As for our main aim, we have shown a significantly higher number of patients stressed with adenosine only to have sub-diaphragmatic activity compared to those who had added exercise ($p = 0.025$). All patients with such uptake had faulty automatic ROI's and subsequently abnormally low LVEF, resulting in higher frequency of manual adjustment of ROI's. After manual adjustment, the new values of LVEF were significantly higher than pre-adjustment values in groups A and B ($p = 0.0001$ and $p = 0.0014$ respectively).

We conclude that adding low-level exercise to adenosine, during stress gated SPECT can significantly improve the automatic selection of left ventricular ROI's, and, subsequently the calculation of LVEF and thereby reduce the frequency of manual adjustment of ROI's. This may have a big impact on the workload in a busy department.

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