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Cardiac displacement during ^{13}N-Ammonia myocardial perfusion PET/CT: comparison between adenosine and regadenoson induced stress

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Abstract

Purpose: In this study, differences are investigated in cardiac displacement during adenosine stress versus regadenoson stress in ^{13}N-Ammonia ($^{13}NH_3$) MP PET/CT scans.

Methods: A total of 61 MP PET/CTs were acquired using either adenosine (n=30) or regadenoson (n=31) as a stressor. For both groups, cardiac displacement during rest and stress was measured three-dimensionally, relative to either a fixed reference frame or the previous frame, in each 1-minute frame of a list-mode PET acquisition of 25 minutes. All stress scans were additionally evaluated for the presence of motion artifacts. Also, patient tolerability and occurrence of various side effects were compared between groups.

Results: Significantly larger cardiac displacement during stress was detected in the adenosine group as compared to the regadenoson group, reflected by both maximal cardiac displacement (p=0.022) and mean cardiac displacement (p=0.001). The duration of the movement was typically shorter in the regadenoson group. Frames with cardiac displacement ≥5 mm were observed nearly twice as frequent when using adenosine instead of regadenoson.

Conclusions: The displacement during regadenoson stress is of lower amplitude and lasts shorter, and may therefore contribute to the lower incidence of motion artifacts on regadenoson compared to adenosine induced stress PET/CT scans.

Keywords: myocardial perfusion PET/CT, ammonia, motion artifacts, adenosine, regadenoson, pharmacologic stress

Introduction

In the past decade, increased availability of PET/CT has led to a gradual shift from conventional myocardial perfusion SPECT towards myocardial perfusion PET/CT (MP PET/CT), using a variety of tracers such as $^{13}NH_3$, $H_2{}^{15}O$, ^{82}Rb. Apart from superior image resolution and decreased radiation burden for patients, advantages of MP PET/CT over conventional SPECT are the ability to measure dynamic myocardial blood flow (MBF) and cardiac flow reserve (CFR) during stress and rest *(1-3)*. Not only can this strengthen a diagnosis of focal ischemia but it also assists detection of global ischemia in balanced significant three-vessel coronary artery stenosis, an important pitfall in conventional myocardial perfusion SPECT *(4)*. On the other hand, MP PET/CT is vulnerable to patient motion, which may result in artifacts or problems in attenuation correction (AC) algorithms *(5,6)* which could lead to false image interpretation and false positive test results. Since MBF measurements and static images of myocardial perfusion are acquired during stress, physical exercise tests are seldom performed in this type of imaging. Instead, pharmacologic stress protocols are utilized using stressors such as adenosine, regadenoson, dipyridamole or dobutamine, which are all FDA approved for this purpose.

Adenosine is the most commonly used coronary vasodilator in myocardial perfusion imaging, has a short half-life of less than ten seconds and non-selectively activates all adenosine receptor subtypes. A variety of side effects including bronchoconstriction can be triggered, which may lead to anxiety and undesirable movement of patients during the pharmacologic stress *(7,8)*. A recent study by Hunter and co-workers has demonstrated that mild to moderate patient motion occurs in over 60% of all MP PET/CTs using adenosine *(9)*. Patient motion and resulting cardiac displacement had highly detrimental effects on MBF calculations. Computer phantom simulations have also demonstrated that voxel based errors can approach up to 500% in extreme scenarios and larger MBF measurement errors have been shown to occur with larger magnitudes of patient motion *(9)*.

A relatively new addition to the pharmacologic testing arsenal is the adenosine receptor agonist regadenoson (Lexiscan, Rapiscan), which has a higher affinity for the A_{2a} receptor but much lower affinity for the other adenosine receptors subtypes *(10)*. As a consequence, effects on the airways are reduced compared to adenosine, especially in patients with chronic obstructive pulmonary disease (COPD) *(11)*, who are prone to develop severe adverse reactions to adenosine. The biological half-life of regadenoson is two to three minutes and thus substantially longer than that of adenosine. However, regadenoson could be a more patient friendly option given its favorable binding characteristics and ease of administration *(12)*.

A reduction of cardiac displacement during $^{13}NH_3$ PET/CT studies would improve the accuracy of the diagnosis. Since regadenoson is known to produce less side effects in patients during pharmacologic stress tests, it can be hypothesized that less patient motion would be observed during MP PET/CT procedures when regadenoson is used instead of adenosine. A recent retrospective study by Memmott et al. demonstrated this using ^{82}Rb MP PET/CT *(13).*

In the present prospective study, patient motion during dynamic $^{13}NH_3$ PET/CT acquisition is compared between two clinical, age and gender-matching cohorts of patients subjected to either adenosine or regadenoson stress. Also, occurrence of motion artifacts in the attenuation corrected $^{13}NH_3$ PET/CTs and experienced side effects of the pharmacologic stressors are compared.

Materials and methods

Patient inclusion and preparation

From January 2016 till February 2016, 61 patients, all referred for $^{13}NH_3$ MP PET/CT, were prospectively included in the study. Thirty patients received adenosine as the pharmacologic stressor, and 31 patients received regadenoson. All patients gave written informed consent for use of their anonymous data for scientific purposes. Since both pharmaceutics are FDA approved and commonly used as stress test agents with comparable efficacy, the examination was covered by standard care. Besides the standard imaging protocol and clinical management no additional measurements or actions affecting the patient were performed. The study was approved by the institutional research board and approval of the local ethical committee for the present study was not necessary since the study does not fall within the scope of the Dutch Medical Research Involving Human Subjects Act (section 1.b WMO, 26th February 1998).

Patients were asked to remain sober (except for water) for six hours before the examination. Patients suffering from diabetes mellitus however, were allowed to eat, drink and use insulin as usual. Caffeine-containing beverages were not allowed for 24 hours for all patients. Also, patients were not allowed to use dipyridamole and methotrexate derivatives 12 hours (regadenoson) or 24 hours (adenosine) before the procedure. Calcium channel and beta-blockers could be taken as prescribed by the cardiologist. An intravenous line was inserted in one arm for injection of either adenosine or regadenoson and in patients receiving adenosine, an additional intravenous line was inserted in the contralateral arm for the $^{13}NH_3$ injection when possible. None of the patients were known with COPD.

Image acquisition

All images were acquired using a Biograph 16 TruePoint PET/CT system (Siemens Medical Solutions, Erlangen, Germany), equipped with a 16-slice CT and a PET scanner with four rings of lutetium oxyorthosilicate detectors. A low-dose CT scan (130 kVp, 25 ref.mAs, pitch 0.95) was performed without breath-holding command prior to a 25-minute PET acquisition performed in list mode. Simultaneously with the initiation of the PET acquisition (*t*=0 min), 305±4 MBq of $^{13}NH_3$ was rapidly injected intravenously to obtain PET images at rest. This was followed by the administration of the stressor using the second intravenous line, when available. In case of adenosine, this was done after *t*=12 min with a dose of 140 µg/kg/min during 6 min. In case of regadenoson, this was done after *t*=14:20 min using a single bolus of 400 µg (5 mL in 10 sec) followed by a 10 mL saline flush (in 10 sec). At *t*=15 min, a second dose of 394±3 MBq $^{13}NH_3$ was administered. Blood pressure was automatically measured twice during the procedure at one minute after each $^{13}NH_3$ administration.

Image reconstruction

Standard static, dynamic and 16-bin ECG-gated reconstructions were obtained as well as 25 additional dynamic reconstructions (60 seconds per frame, TrueX reconstruction algorithm including a point spread function correction) for analysis of cardiac movement during the PET acquisition. These frames were generated with a 168x168 matrix, slice thickness 3 mm, zoom 2, Gaussian filter with a full width at half maximum of 5 mm, 4 iterations and 8 subsets. Series of frames were assigned as the various acquisition components which are displayed in Figure 1.

Image analysis

A cardiac specific motion correction algorithm developed by Siemens Molecular Imaging (Oxford, United Kingdom) was used to automatically detect displacement of the myocardium between dynamic frames. Cardiac displacement was determined by rigid image registration between each of the frames and a reference frame. Frame 3 (first available PET image after the AC CT scan) was used as the reference frame to determine cardiac movement by the automatic motion correction software, since myocardial activity was still absent in frame 1 and 2 and obscured by blood pool activity. Myocardial visualization was also hampered by blood pool activity in frame 16, which was therefore excluded from analysis. Both rotation and translation of the registration matrix were evaluated visually by

overlaying the motion corrected target image on the source image in comparison with the non-motion corrected image pairs. Cardiac displacement between frames was measured in millimeters in three dimensions, either positive or negative, using the automatic motion correction algorithm. Positive displacement along the X-axis was defined as movement of the patient from right to left and positive displacement along the Y-axis from ventral to dorsal. A positive cardiac displacement along the Z-axis was defined as movement in caudal to cranial direction (see insert in Figure 2). The length of a single displacement vector in 3D space was then calculated from the cardiac displacement obtained in three directions and verified visually. As an internal validation of the algorithm, displacement of the reference frame against itself was determined for all datasets and was below 0.3 mm on average in all axes. Occasionally, frame 2 or 4 was used as the reference frame when automated myocardial contour detection was suboptimal in frame 3. Additionally, cardiac displacement was also calculated relative to the previous available frame in order to obtain a more detailed description of the displacement pattern.

Cardiac displacement during the rest acquisition was compared between the adenosine and regadenoson group and maximum and mean of the cardiac displacement during the rest acquisitions were obtained within frames 2-12. Next, the cardiac displacement during pharmacologic stress was evaluated between those groups. Maximum and mean of the displacement during stress acquisitions were obtained within frames 13-25 for adenosine and frames 15-25 for regadenoson. Additionally, cardiac displacement was compared between the rest acquisition and the pharmacologic stress acquisition of both the adenosine and regadenoson groups. The maximal displacement during each acquisition was categorized as minor (<5 mm), medium (5-10 mm) or large (>10 mm) relative to the reference and previous frame. The number of patients displaying medium and large cardiac displacement during pharmacologic stress was compared between the adenosine and regadenoson group. Also, the total number of frames that showed medium or large cardiac displacement was counted in all PET/CT procedures for both study groups as a measure of duration of cardiac displacement during pharmacologic stress.

Visual appraisal of motion artifacts on PET/CT scans

All anonymized $^{13}NH_3$ myocardial PET/CT stress scans were reviewed visually by two experienced nuclear medicine physicians, blinded to the used protocol, for presence of motion artifacts on static images. For this analysis, AC and non-attenuation corrected (NAC) static images were compared and dynamic series were reviewed when necessary. Detected artifacts were categorized in consensus as small, intermediate or large.

Survey of side effects

Patients were interviewed by a physician assistant after completion of the procedure, using a standard questionnaire. Observed symptoms were categorized as absence of symptoms, typical chest pain, respiratory, gastrointestinal or vasodilator symptoms or as other. Also, the general degree of discomfort of the procedure was categorized as very inconvenient, inconvenient, tolerable with little discomfort, or as no discomfort at all.

Statistical analysis

SPSS v 20.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The Kolmogorov-Smirnov test was used to evaluate normal distribution of data. Continuous variables with normal distribution are presented as mean ± standard deviation (SD) and categorical variables as frequencies with percentages. Student T-tests were used for comparison of variables with a normal distribution. Mann-Whitney tests were performed to detect differences in the non-normally distributed cardiac movement during the various acquisitions and data were additionally expressed as median and interquartile range (IQR). For analysis of the relationship between categorical variables Pearson Chi-Square tests were performed. Where appropriate tests were two-sided and in all tests, p-values ≤ 0.05 were considered significant.

Results

Patient population

A total of 61 patients referred for MP PET/CT were included. Baseline characteristics are detailed in Table 1. There were no significant differences between mean age, gender, average BMI and Duke Clinical Score *(14-16)* of the adenosine and regadenoson groups.

Cardiac movement during stress acquisition

A patient example of cardiac movement in X, Y and Z direction relative to the reference frame at various time points during of an adenosine stress test is displayed in Figure 2.

A significantly larger cardiac displacement relative to the previous available frame was detected in patients subjected to adenosine stress compared to those receiving regadenoson. This is reflected in both maximal cardiac

displacement (mean±SD 8.1±3.7 vs. 6.1±2.3 mm; p=0.022) and mean cardiac displacement (median and IQR 2.7 (2.1-3.2) vs. 2.0 (1.5-2.4) mm; p=0.001), as represented by the total vector, see Tables 2, 3 (maximum cardiac displacement) and Figure 3a (mean cardiac displacement). There were no significant differences in maximum (mean±SD 3.8±1.9 vs. 3.8±1.5 mm; p=0.593) and mean cardiac displacement (p=0.155) between rest acquisitions of the adenosine versus the regadenoson group (see Tables 2, 3 and Figure 3b). Significant larger mean cardiac displacement was detected during the stress versus the rest acquisition for both the adenosine (p<0.001) and regadenoson (p<0.001) group.

Cardiac displacement relative to the reference frame is displayed in Tables 2 and 3 and Figures 3c and 3d. A significant difference in maximum cardiac displacement was detected between both groups (mean±SD 11.6±5.2 for adenosine vs. 8.6±3.0 mm for regadenoson; p=0.014). Although both median and IQR of mean cardiac displacement are higher for the adenosine stress datasets, a significant difference was present only in Y direction during stress (p=0.029).

The mean vector of cardiac displacement during the entire acquisition and the absolute values of the mean displacement in three dimensions are plotted in Figure 4 for the adenosine (Figures 4a and 4c) and regadenoson (Figures 4b and 4d) group. The plotted data clearly shows increased displacement during administration of adenosine compared to tests performed with regadenoson. The largest displacement of the heart is present in the Z-axis, especially in the adenosine group and to a lesser extent, also in the Y-axis. The figure also shows that cardiac displacement relative to the reference frame persists longer in the adenosine compared to the regadenoson group. Substantial cardiac displacement, when defined as displacement ≥5 mm relative to the reference frame, is present during 8 consecutive minutes in the adenosine versus 3 minutes in the regadenoson group.

Compared to the previous available frame, medium displacement (5-10 mm) was detected in more than half of the patients in both the adenosine and regadenoson groups (Table 4). Large displacement (>10 mm) of the heart, relative to the reference frame, was more prevalent in the adenosine group. The total number of analyzed frames of the adenosine group yielded a small but higher fraction of frames with medium cardiac displacement relative to the previous frame, as opposed to the regadenoson group. Large cardiac displacement compared to the previous frame was detected in only a few frames of the adenosine group and in only one frame of the regadenoson group (Table 4). Similar results are demonstrated when using frame 3 as a reference, although relatively more patients of the adenosine group demonstrated large cardiac displacement (Table 4). The number of frames displaying medium or

large cardiac displacement relative to the reference frame, as a measure for the duration of that displacement, was higher in the adenosine compared to the regadenoson group during stress.

Both adenosine and regadenoson stress acquisitions demonstrated a peak in cardiac displacement after administration of the stressor. However, the cardiac displacement is generally larger during adenosine stress (Tables 2, 3 and Figures 3a, 3c, 4).

Visual appraisal of motion artifacts on PET/CT scans

Compared to the adenosine group, less motion artifacts were encountered on stress $^{13}NH_3$ PET/CTs in patients that received regadenoson as a stressor; in 14/30 (46.7%) vs. 9/31 (29.0%) (p=0.192) patients, respectively. No artifacts were graded as large. Medium sized artifacts were found in 2/30 (6.7%) patients of the adenosine group, compared to none in the regadenoson group. The remainder of the patients displayed small artifacts in 12/30 (40.0%) patients of the adenosine and 9/31 (29.0%) of the regadenoson group.

Patient tolerability to adenosine and regadenoson

The patient survey did not show differences in experienced side effects between the adenosine and regadenoson group (Table 5). Respiratory symptoms were reported by 16 (53.3%) patients in the adenosine group and 11 (35.5%) patients in the regadenoson group (p=0.095). Typical chest pain, gastrointestinal side effects, vasodilatation related side effects and a variety of other side effects in the adenosine vs. regadenoson group were reported by patients of both groups, and no significant differences were found. The overall patient experience with respect to the pharmacologic stressors was also similar for adenosine and regadenoson group (p=0.428), as patients graded both test protocols as equally inconvenient.

Discussion

Cardiac displacement during acquisition is the principal source of artifacts in MP PET/CT and may lead to erroneous interpretation. It is well known that CT-based AC can introduce artifacts in PET images due to misregistration *(17)*. The present study points out that cardiac displacement occurs more frequently, with higher amplitude and longer duration when using adenosine compared to regadenoson, possibly due to physical complaints, anxiety or panic during the stress study. Compared to regadenoson, motion artifacts were approximately 50% more

prevalent in adenosine stress acquisitions and present in almost 50% of all scans. Before MP PET/CT each patient should be positioned comfortably and instructed thoroughly to reduce cardiac displacement due to patient movement. During stress acquisition, a nuclear medicine physician or a well-trained technician should be able to communicate with the patient, not only for safety reasons but also to reassure patients, which may help to avoid anxiety or panic. Despite such precautionary measures, artifacts arising from patient or cardiac movement cannot always be prevented. Another, more intrinsic cause for cardiac displacement during pharmacologic stress may be the well-known urge to breathe deeply *(18,19)* during administration of the stress test agent, which may lead to a temporary alteration of the anatomical position of the heart due to diaphragm displacement. While impossible to prove this with the present data, the observed displacement is in agreement with this, especially but not exclusively in the adenosine group. Literature on motion artifacts in MP PET/CT imaging is scarce, particularly for $^{13}NH_3$ MP PET/CT performed with adenosine or regadenoson. However, our study is in line with a recently published retrospective study by Memmott et al., in which data acquisition was started at 210-240 seconds after initiation of adenosine or 40 seconds after regadenoson injection *(13)*. The present study reports cardiac movement in three dimensions in a wider time frame, i.e. during and between rest and stress acquisitions and this yields additional insight in the movement pattern at early stages of the stress procedure. We report the largest cardiac shift along the Z-axis, directly after initiation of adenosine infusion and to a lesser extent after regadenoson administration, which could result from a change in breathing pattern. By the end of the adenosine infusion, we also observe a movement of the heart to its initial position.

When cardiac displacement occurs after CT acquisition but before PET acquisition, the AC map can usually be adjusted properly using the reconstruction software by applying a registration matrix between PET and CT images. This matrix can be obtained by manual or automatic realignment of the NAC PET images and CT images. However, if patient or solely cardiac movement occurs during PET acquisition it is impossible to apply proper CT AC to the entire acquired PET dataset. When this happens, one can consider reconstructing two datasets (before and after the displacement) for both static and gated images and to apply an applicable registration matrix for better AC. There are, however, disadvantages to this approach (for instance less counts) and it does not apply to dynamic studies. It is also ineffective when multiple movements occur during PET acquisition. Detrimental misalignment effects have

been described previously for both static PET acquisitions (AC induced artifacts) *(17)* and dynamic acquisitions (errors in MBF calculations) *(20)*.

Generation of frame specific registration matrices could potentially solve the problem of misregistration due to cardiac movement for dynamic frames with AC. To date, such software is unavailable, at least for Siemens PET/CT systems. At present, only one registration matrix can be applied to all dynamic frames, which may lead to AC errors at specific time points. Another problem for the accuracy of MBF calculations is the inability to correct for cardiac displacement during early dynamic frames. This potentially leads to misplacement of myocardial and intraventricular regions of interest when movement occurs during this phase. Obviously, this could affect the measured time activity curves (TAC) and MBF calculations. Therefore, cardiac displacement reduction during PET acquisition improves accuracy of the diagnosis in cardiac PET. PET/MRI scanners could also potentially solve the problem with misalignment. Simultaneous acquisition of MR and PET images can provide a frame specific MR-based attenuation correction for each dynamic PET frame. This would avoid errors in MBF calculations introduced by wrong attenuation correction. Currently, in the absence of proper AC for individual dynamic frames, a quantitative indication of the average and maximum cardiac displacement between reconstructed dynamic frames could be useful for clinicians to assess the scan quality in addition to the visual appraisal of the blood input function (BIF). Datasets with large cardiac displacement could be considered as less reliable. Such quantitative analysis could easily be incorporated in commercial MBF analysis software but is, to our knowledge, unavailable at present.

Other options for motion artifact reduction include replacement of both adenosine and regadenoson with other pharmacologic stressors, such as dobutamine or dipyridamole. Dobutamine is impractical for routine use in $^{13}NH_3$ MP PET/CT since it is uncertain at what time point the required heart rate is achieved after initiation of the stressor. Also, in a paper by Hunter et al. *(9)* motion artifacts were reported (in up to 60% of all clinical scans) together with detrimental effects on MBF calculations, using the indirect coronary vasodilator dipyridamole as a stressor. While dipyridamole less frequently leads to side effects, especially less shortness of breath, these effects are generally less tolerated and last longer, due to the longer biological half-life of the pharmaceutical (40 minutes versus <10 seconds). Side effects may last for 15-25 minutes, occasionally requiring theophylline to terminate the effects, whereas effects of adenosine resolve rapidly within minutes after the test *(21)*. Besides, Vasu and co-workers demonstrated less efficacy of dipyridamole in cardiovascular magnetic resonance imaging compared to both

adenosine and regadenoson yielding lower MBF and CFR values as compared to regadenoson or adenosine induced stress *(22)*.

A limitation of the present study is the relatively small cohort of 61 patients. Statistical power appears to be insufficient to draw solid conclusions on differences between subgroups regarding patient symptoms or scan results by visual appraisal, in particular. Correlation between the experienced degree of discomfort and extent of cardiac displacement appeared non-existent in the relatively small cohort of the present study (r^2 was 0.12 for adenosine and 0.01 for regadenoson). Also, heterogeneity of the cohorts existed, since some patients were already known with cardiovascular disease, although movement patterns appeared to be similar. Another source of error could be the residual activity correction algorithm, which is based on a background subtraction and combined modeling approach for estimation of rest and stress blood flow. The residual activity from the rest injection is quantified using the first frame of the stress study (acquired during 30 seconds before the stress injection). The BIF and TAC obtained from the stress acquisition are being corrected by subtracting the residual activity from all frames of the decay corrected TACs and BIF *(23)*. In daily clinical practice, this effectively eliminates interference of residual activity in our time-efficient MP PET/CT protocol. Despite extensive local experience with $^{13}NH_3$ MP PET/CT in more than 2500 studies thus far, response and observer bias cannot be ruled out completely. Nonetheless, the findings of the present study may be relevant and of assistance in stress protocol design in institutions that are or will be performing this type of PET/CT examinations.

Adenosine is an effective and cheap stress test agent and has been produced by large numbers of pharmacies for decades. After registration in 2008, regadenoson was added to the pharmacologic stressor inventory and has since then been used frequently in patients with COPD in whom less side effects are observed *(24)*. Unfortunately, regadenoson is considerably more expensive and whether the benefit of less motion artifacts and better patient tolerability outweigh the substantial higher costs of regadenoson remains to be determined. Future studies on cost-effectiveness need to include factors such as savings on additional diagnostic procedures like coronary angiography or benefits from more accurate treatment like revascularization procedures.

Conclusion

Patients undergoing adenosine MP PET/CT demonstrate a significant different cardiac displacement pattern compared to patients receiving regadenoson. The cardiac displacement pattern during regadenoson stress has lower amplitude, lasts shorter, and may contribute to the lower incidence of motion artifacts on regadenoson compared to adenosine induced stress PET/CT scans.

Disclosure

Conflicts of interest

None.

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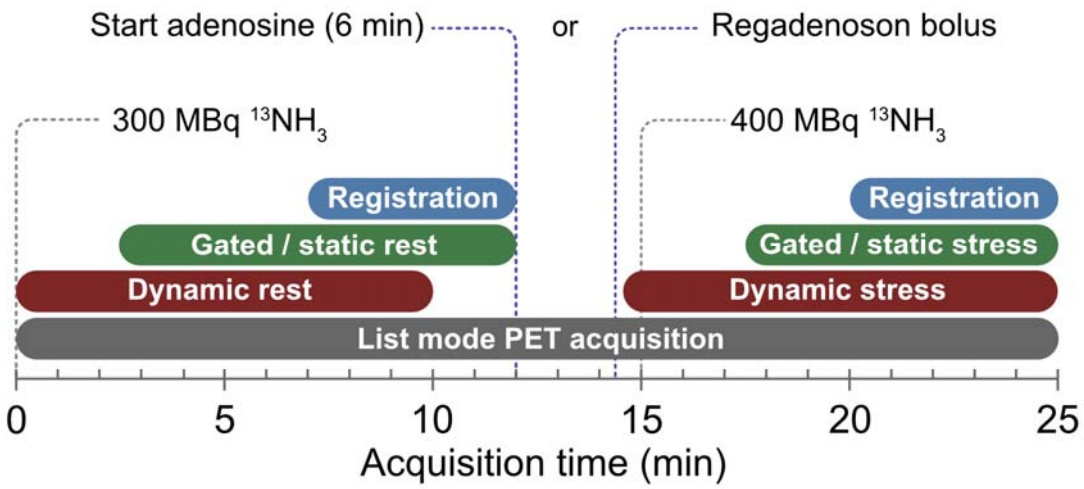
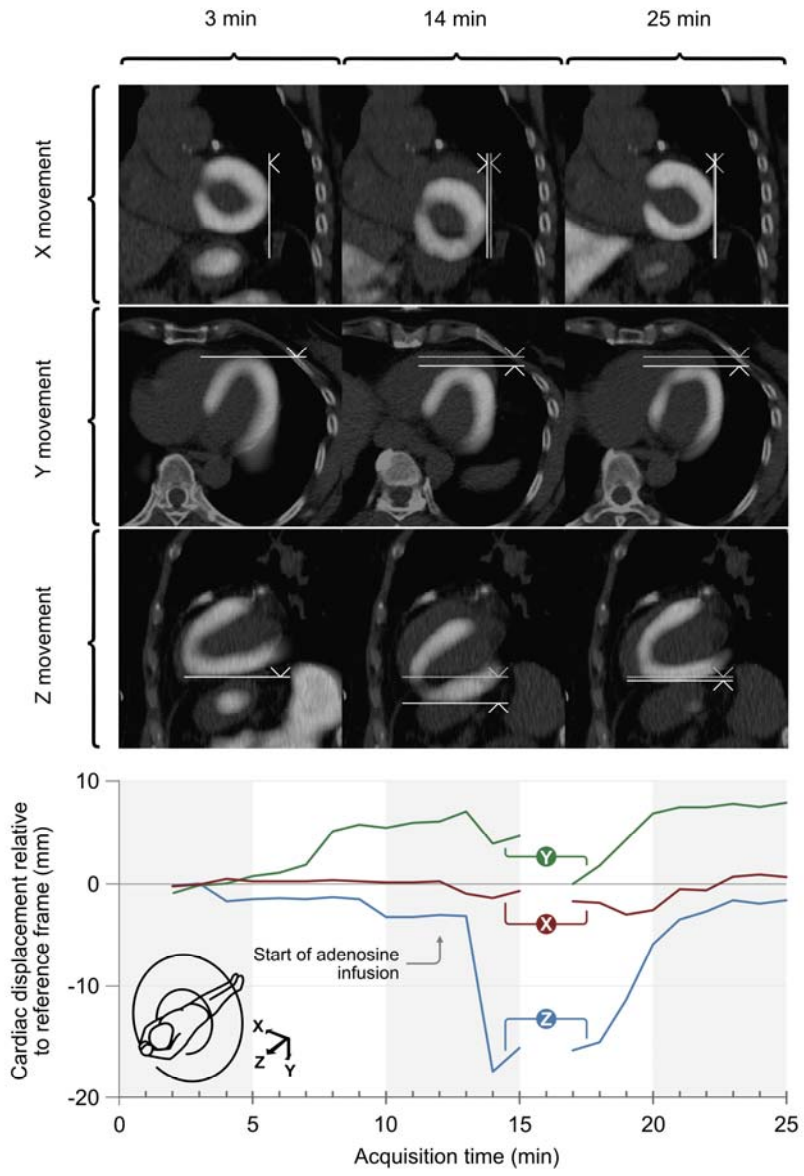
FIGURE 1 CAPTION



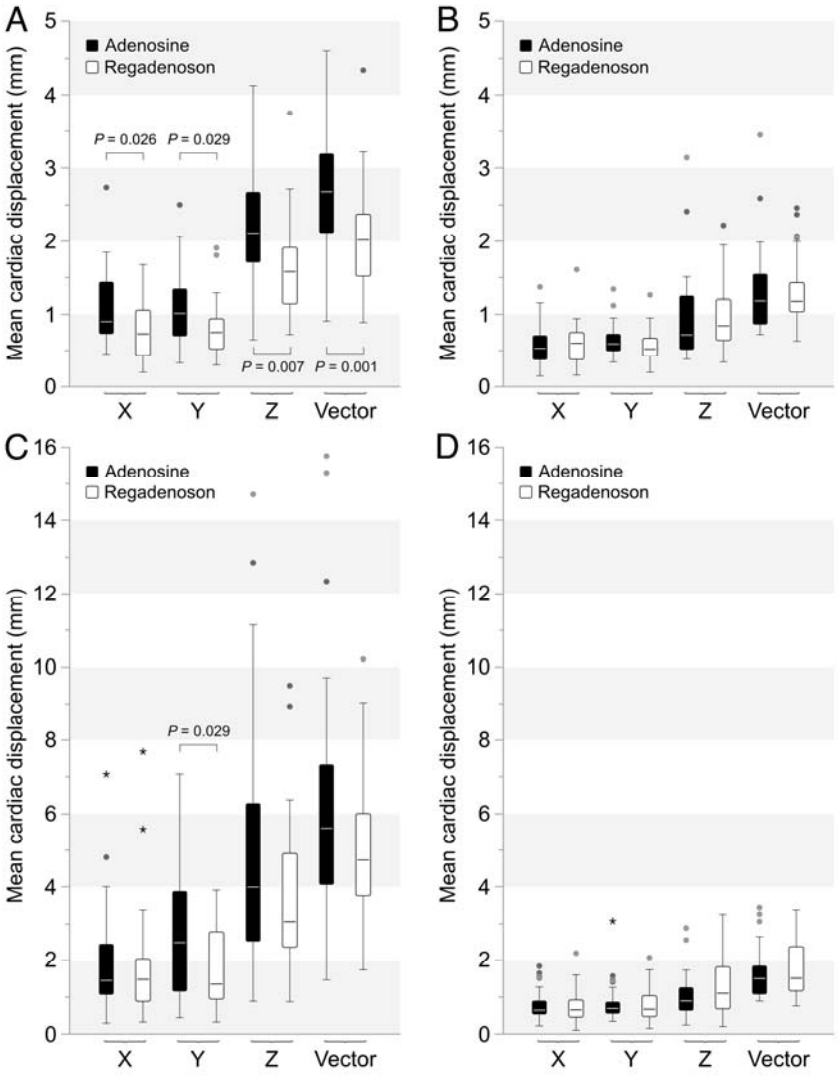
Components of the rest and stress acquisitions (adenosine or regadenoson).

FIGURE 2 CAPTION



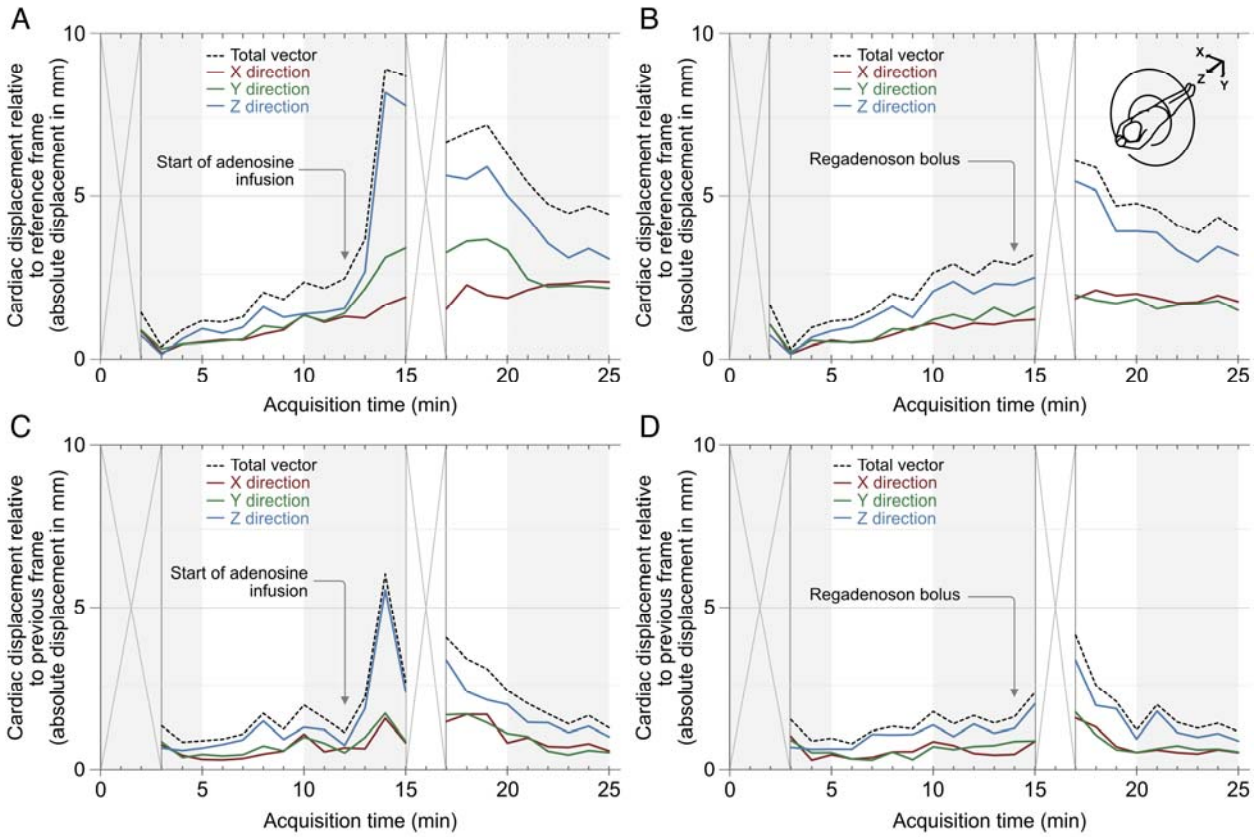
Upper panel: Example of cardiac displacement during adenosine stress. Cardiac displacement is depicted in coronal (upper row of tiles), transverse (middle row), and sagittal (lower row) planes in X, Y and Z direction, respectively. Images represent data obtained at 3 minutes after scan initiation (frame 3; reference frame), at 14 minutes (2 minutes after initiation of adenosine) and at 25 minutes (last frame of the stress acquisition). The solid vertical and horizontal marking lines in each tile of the 14 and 25-minute series represent cardiac displacement relative to the initial position of the heart (dotted line). *Lower panel:* Cardiac displacement in X, Y and Z direction in the presented patient during the entire scan, relative to the reference frame (at 3 minutes after the initiation of the scan).

FIGURE 3 CAPTION



Median with interquartile ranges (IQR) of the mean cardiac displacement in X, Y and Z direction and total displacement vector length for both adenosine and regadenoson. Panel **a** displays displacement during stress relative to the previous available frame and panel **b** shows displacement in rest. Panel **c** demonstrates cardiac displacement relative to the reference frame (frame 3) during stress and panel **d** shows the displacement relative to the reference frame at rest. Statistical analysis performed using Mann-Whitney tests.

FIGURE 4 CAPTION



Cardiac displacement during stress and rest acquisitions in X, Y and Z direction and total displacement vector length (dotted line). Data represent the means of all patients and are given relative to the reference frame (frame 3) in panel **a** and **b**, and relative to the previous frame in panel **c** and **d**. Panel **a** and **c** represent cardiac displacement during adenosine and panel **b** and **d** represent cardiac displacement during regadenoson stress. Gaps in plots are the result of exclusion of frames due to high blood pool activity after injection of $^{13}NH_3$, see text.

TABLE 1
Baseline characteristics, known risk factors, stress test parameters and clinical PET/CT diagnosis. Statistical analyses by Mann-Whitney tests by default, or else, as indicated.

Baseline characteristics	**Adenosine**	**Regadenoson**	**P-value**
Patients included (Male/Female)	30 (15/15)	31 (15/16)	0.901
Age (mean years ± SD)	68 ± 10	67 ± 9	0.608†
BMI (mean BMI ± SD)	28.1 ± 4.8	27.1 ± 4.9	0.116
Duke Clinical Score (mean % ± SD)*	62 ± 33	55 ± 32	0.243
Risk factors			
Diabetes Mellitus [n (%)]	0 (0.0%)	6 (19.4%)	0.012
Family history of CAD [n (%)]	7 (23.3%)	8 (25.8%)	0.824
Hypertension [n (%)]	18 (60.0%)	14 (45.2%)	0.250
Smoking [n (%)]	4 (13.3%)	6 (19.4%)	0.529
Previous myocardial infarction [n (%)]	13 (43.3%)	5 (16.1%)	0.021
Previous percutaneous coronary intervention [n (%)]	12 (40.0%)	6 (19.4%)	0.080
Previous coronary artery bypass grafting [n (%)]	2 (6.7%)	2 (6.5%)	0.973
Stress test parameters			
Max heart rate during stress (mean bpm ± SD)	91 ± 18	94 ± 18	0.704
Percentage heart rate of max. (mean % ± SD)	59.1 ± 9.9	61.1 ± 12.0	0.367
Systole at peak stress (mean mmHg ± SD)	125.1 ± 15.8	136.1 ± 14.8	0.602
Diastole at peak stress (mean mmHg ± SD)	67.5 ± 10.5	71.0 ± 9.5	0.611
PET/CT results			
No ischemia or infarction [n (%)]	17 (56.7%)	22 (70.9%)	
Ischemia [n (%)]	10 (33.3%)	3 (9.7%)	0.141‡
Infarction [n (%)]	3 (10.0%)	6 (19.4%)	
Artifacts			
Motion artifacts static stress [n (%)]	14 (46.7%)	9 (30.0%)	0.192

* In both groups, the Duke Clinical Score was missing in two patients

† Independent-samples t-test

‡ Chi-square test

TABLE 2
Maximal displacement in three axes during stress acquisitions (frame 13-25 for adenosine and frame 15-25 for regadenoson) using the **previous frame** (left) or **frame 3** (right) as a reference. Analysis for displacement relative to previous frame was performed with Mann-Whitney tests. Analysis for displacement relative to frame 3 was done using the independent samples t-test.

Maximal displacement during stress acquisitions	**Relative to previous frame**			**Relative to frame 3**		
	Adenosine	**Regadenoson**	**P-value**	**Adenosine**	**Regadenoson**	**P-value**
Negative X direction*	-2.9 ± 1.8	-2.3 ± 1.5	0.083	-2.5 ± 1.9	-2.9 ± 2.3	0.435
Negative Y direction*	-3.1 ± 1.8	-2.3 ± 1.5	0.024	-4.8 ± 3.3	-3.1 ± 2.0	0.012
Negative Z direction*	-6.4 ± 3.7	-4.9 ± 2.2	0.123	-9.9 ± 5.3	-7.1 ± 3.6	0.048
Positive X direction*	2.7 ± 1.4	1.8 ± 1.0	0.007	2.2 ± 2.6	0.7 ± 1.5	0.063
Positive Y direction*	2.6 ± 1.4	2.2 ± 1.7	0.082	0.2 ± 2.3	0.7 ± 1.3	0.030
Positive Z direction*	4.9 ± 2.5	3.7 ± 1.7	0.034	0.4 ± 3.2	0.6 ± 2.3	0.229

* in mean mm ± SD

TABLE 3
Maximal displacement as vector length during rest and stress acquisitions using the **previous frame** (left) or **frame 3** (right) as a reference. Analysis performed with Mann-Whitney tests.

Maximal displacement during rest and stress acquisitions	**Relative to previous frame**			**Relative to frame 3**		
	Adenosine	**Regadenoson**	**P-value**	**Adenosine**	**Regadenoson**	**P-value**
Vector length rest*	3.8 ± 1.9	3.8 ± 1.5	0.593	4.1 ± 1.7	4.4 ± 2.6	0.971
Vector length stress*	8.1 ± 3.7	6.1 ± 2.3	0.022	11.6 ± 5.2	8.6 ± 3.0	0.014

* in mean mm ± SD

TABLE 4
Total number of frames of all patients with minor, medium and large displacement during stress acquisition using the **previous frame** (left) or **frame 3** (right) as a reference. Analysis performed with Chi-square tests.

Total number of frames or number of patients	Relative to previous frame			Relative to frame 3		
	Adenosine	Regadenoson	P-value	Adenosine	Regadenoson	P-value
Frames <5 mm stress [n (%)]	1025 (94.9%)	1088 (97.5%)		861 (79.7%)	991 (88.8%)	
Frames 5-10 mm stress [n (%)]	51 (4.7%)	27 (2.4%)	0.005	174 (16.1%)	112 (10.0%)	<0.001
Frames >10 mm stress [n (%)]	4 (0.4%)	1 (0.1%)		45 (4.2%)	13 (1.2%)	
Patients with minor displacement < 5 mm [n (%)]	10 (13.3%)	12 (38.7%)		4 (13.3%)	7 (22.6%)	
Patients with medium displacement 5-10 mm [n (%)]	16 (53.3%)	18 (58.1%)	0.352	11 (36.7%)	20 (64.5%)	0.007
Patients with large displacement >10 mm [n (%)]	4 (13.3%)	1 (3.2%)		15 (50.0%)	4 (12.9%)	

TABLE 5
Reported symptoms during stress acquisition. Statistical analysis performed by Pearson Chi-Square test to identify differences during the stress vs. rest acquisition.

Symptoms during stress acquisitions	Adenosine*	Regadenoson	P-value
None [n (%)]	6 (19.4%)	9 (15.3%)	0.357
Typical chest pain [n (%)]	10 (33.3%)	8 (25.8%)	0.409
Respiratory [n (%)]	16 (53.3%)	11 (35.5%)	0.095
Gastrointestinal [n (%)]	5 (16.7%)	7 (22.6%)	0.653
Vasodilation [n (%)]	12 (40.0%)	14 (45.2%)	0.859
Other [n (%)]	3 (10.0%)	3 (9.7%)	0.895
General degree of discomfort (mean ± SD)†	2.9 ± 1.1	2.6 ± 1.1	0.428

***** Two surveys were missing in the adenosine group.
† The general degree of discomfort was expressed in a number from 1 (no discomfort at all) to 5 (very inconvenient). In both groups, one patient gave a deviant answer, and both were excluded from analysis.