# No need for frame-wise attenuation correction in dynamic Rubidium-82 PET for myocardial blood flow quantification

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***Background.*** **Regadenoson-induced stress causes a repositioning of the heart, myocardial creep, in half of the patients undergoing Rubidium-82 (Rb-82) positron emission tomography (PET). As a result, misalignment of dynamic PET and computer tomography (CT) may occur, possibly affecting CT-based attenuation correction (AC) and thereby PET-based myocardial blood flow (MBF) quantification. Our aim was to determine the need for frame-wise PET-CT AC to obtain reliable MBF measurements.**

***Methods.*** **31 Out of 64 consecutive patients had myocardial creep during regadenoson-induced stress Rb-82 PET-CT and were included. Prior to PET image reconstruction, we applied two AC methods; single PET-CT alignment and frame-wise alignment in which PET time-frames with myocardial creep were individually co-registered with CT. The PET-CT misalignment was then quantified and MBFs for the three vascular territories and whole myocardium were calculated and compared between both methods.**

***Results.*** **The magnitude of misalignment due to myocardial creep was 13.8 ± 4.5 mm in caudal-cranial direction, 1.8 ± 2.1 mm in medial-lateral and 2.5 ± 1.8 mm in anterior-posterior direction. Frame-wise PET-CT registration did not result in different MBF measurements ($P \geq .07$) and the magnitude of misalignment and MBF differences did not correlate ($P \geq .58$).**

***Conclusion.*** **There is no need for frame-wise AC in dynamic Rb-82 PET for MBF quantification. Single alignment seems sufficient in patients with myocardial creep. (J Nucl Cardiol 2019;26:738–45.)**

**Key Words: Myocardial blood flow • attenuation correction • PET-CT registration • PET rubidium**

**See related editorial, pp. 747–748**

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| Abbreviations | |
|---|---|
| AC | Attenuation correction |
| BMI | Body mass index |
| CT | Computer tomography |
| MPI | Myocardial perfusion imaging |
| MBF | Myocardial blood flow |
| PET | Positron emission tomography |
| Rb-82 | Rubidium-82 |
| SD | Standard deviation |

## INTRODUCTION

Myocardial blood flow (MBF) quantification is increasingly used in positron emission tomography (PET) myocardial perfusion imaging (MPI) with Rubidium-82 (Rb-82).[1,2] MBF quantification provides valuable additional prognostic information about the extent and functional importance of possible stenosis.[3,4] With the increasing use there is a growing attention for further refinement of acquisition and processing settings as small changes in the dynamic PET data may hamper accurate MBF quantification.[5–7]

Reliable dynamic PET data are needed to accurately quantify the MBF. However, a repositioning of the heart, also known as myocardial creep, occurs typically in half of the patients after pharmacological stress.[5,8] This creep is presumably caused by a decrease in respiration and lung volume and thereby repositioning of the diaphragm and heart after pharmacological stress.[9] As myocardial contours are usually drawn on the last frames, the repositioning may result in a myocardium which lies out of these contours at the beginning of the scan. This misalignment produces errors in the time activity curves (TACs) and eventually in MBF measurements and can partly be overcome by correcting the misalignment for each frame.[5,8,10] This correction is commonly only performed during post-processing on attenuation corrected PET data. However, as the emission data are acquired over several minutes, misalignment of PET and computer tomography (CT) data can occur in the early phase of the PET scan when myocardial creep is present. Consequently, this may affect CT-based attenuation correction (AC) which could constitute a second source of errors in deriving accurate MBF measurements.[11–13] This possible AC error could potentially be overcome by matching the CT and PET data for each individual time-frame prior to data reconstruction.[8,10,14] Therefore, our aim was to determine the effect of frame-wise AC instead of single PET-CT AC on MBF quantification.

## METHODS

### Patient Population

We retrospectively included 64 consecutive patients referred for MPI using Rb-82 PET-CT (GE Discovery 690, GE Healthcare) who underwent rest and regadenoson-induced stress imaging. Next, we excluded 33 patients in whom no myocardial creep was observed according to the criteria described by Koenders et al.[5] In brief, myocardial creep was defined as a misalignment of at least one third of the width of the left ventricular myocardial contour, based on data acquired between 2:30 and 7:00 minutes post injection of Rb-82, and the activity observed in the early PET time-frames. This misalignment had to be present in at least two time-frames of which one had to include the first-pass phase or filling of the left ventricle (LV).[5] This study was retrospective and approval by the medical ethics committee was therefore not required according to Dutch law. Nevertheless, all patients provided written informed consent for the use of data for research purposes.

### Data Processing

All patients were instructed to abstain from caffeine-containing substances for 24 hours and to discontinue dipyridamole containing medication for 48 hours before imaging. A low-dose CT scan was acquired prior to PET imaging during free-breathing to provide an attenuation map of the chest. This CT scan was made using a 5 mm slice thickness, 0.8 seconds rotation time, pitch of 0.97, collimation of 32 × 0.625 mm, tube voltage of 120 kV and tube current of 10 mA. Next, 740 MBq Rb-82 was administered intravenously with a flow rate of 50 mL/min using a Sr-82/Rb-82 generator (CardioGen-82, Bracco Diagnostics, Inc.). After the rest acquisition, we induced pharmacological stress by administrating 400 μg (5 mL) of regadenoson over 10 seconds. After a 5 mL saline flush (NaCl 0.9%) we administered a second dose of 740 MBq Rb-82. Patients responding to regadenoson were defined as having a drop in systolic blood pressure of ≥ 10 mmHg and having an increase in heart frequency ≥ 10. Partial response was defined as patients fulfilling one of the two criteria and non-response was defined as fulfilling none of the criteria. We acquired PET list-mode acquisitions of 7 minutes after both Rb-82 administrations. Dynamic PET datasets were created using 26 time-frames: 12 × 5, 6 × 10, 4 × 20, and 4 × 40 seconds.

### PET-CT Registration and Myocardial Creep

For all stress scans, we applied two types of co-registration with CT prior to image reconstruction of the dynamic PET data with CT-based AC. The first was the single alignment in which PET data acquired between 2:30 and 7:00 minutes were aligned to the CT. This registration was then applied to all 26 PET time-frames. The second type of alignment was a frame-wise co-registration to correct for possible PET-CT misalignments in the early time-frames due to myocardial creep. The

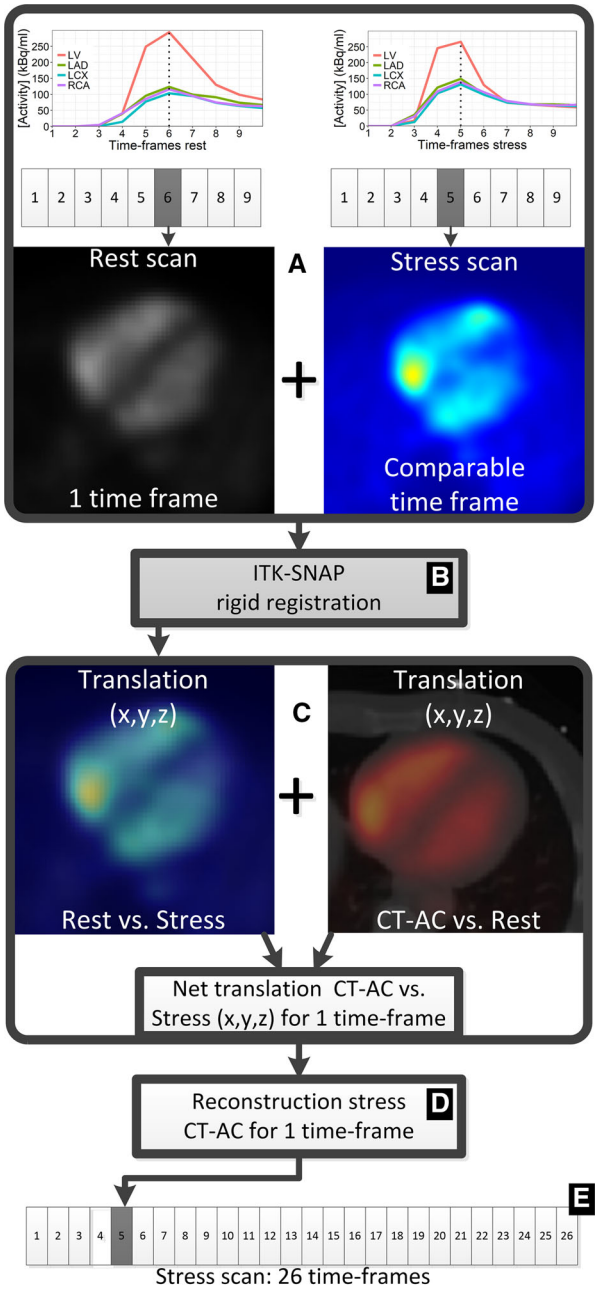


**Figure 1.** Overview of the steps when applying frame-wise attenuation correction in one time-frame with myocardial creep. (**A**) Aligning the rest with the stress time-frame, based on the peak in the activity concentration in the left ventricle. (**B**) The corresponding rest and stress time-frames are rigidly registered in ITK-SNAP to obtain the rest-stress translation. (**C**) The rest-stress translation ($x$, $y$, $z$) is added to the original rest CT-AC translation ($x$, $y$, $z$) resulting in the net CT-AC stress translation ($x$, $y$, $z$) for that time-frame. (**D**) Reconstruction of a new stress time-frame with frame-wise CT-based attenuation correction and (**E**) replacement of this frame with the original time-frame in the dynamic series.

**Table 1.** Baseline characteristics and scan outcome of all 31 patients who underwent clinically indicated PET Rb-82 MPI stress imaging and in which myocardial creep was observed

| **Characteristics** | **(n = 31)** |
|---|---|
| Age (years) | 68.6 ± 10.14 |
| Male gender | 68% |
| Body weight | 84.3 ± 14.0 |
| BMI | 27.4 ± 3.6 |
| Current smoking | 16% |
| Hypertension | 65% |
| Diabetes | 19% |
| Dyslipidemia | 48% |
| Family history | 48% |
| Normal MPI scan | 24 (77%) |
| Ischemic defect | 5 (16%) |
| Irreversible defect | 3 (10%) |
| Summed stress score $\geq 4$[21] | 16 (52%) |
| Summed difference score $\geq 2$[21] | 8 (25.8%) |
| Ejection fraction (stress) | 63.6 ± 12.4 |

Values are presented as mean ± SD or numbers (percentage)
*BMI*, body mass index

PET data of the individual time-frames in which myocardial creep was possibly present were individually aligned to the CT and subsequently reconstructed. To minimize the influence of operator variability for this frame-wise co-registration, we first aligned the rest PET with the stress PET using automatic rigid registration based on image similarity using ITK-SNAP software (version 3.6.0, www.itksnap.org), as shown in Figure 1. To ensure matching stress and rest time-frames with a comparable activity distribution, we matched the stress and rest time-frames with a comparable activity concentrations in the LV based on the TACs. Second, we added the obtained rest-stress PET translation to original rest PET-CT translation for each individual time-frame to obtain the net stress PET-CT translation for the individual time-frames in which myocardial creep was possibly present. We performed this two step process as were unable to directly match the stress PET with the CT during the first-pass phase due to the dissimilarities between the anatomical CT data and functional PET data as a results of the absence of Rb-82 activity during the earlier time-frames.

We compared the derived translations in all three directions; cranial-caudal, medial-lateral and anterior-posterior and derived the difference between both registration methods ($\Delta T$). In addition, the overall translation difference ($\Delta T_{\text{overall}}$) was calculated by:

$$\Delta T_{\text{overall}} = \sqrt{\Delta T^2_{\text{cranial-caudal}} + \Delta T^2_{\text{medial-lateral}} + \Delta T^2_{\text{anterior-posterior}}}.$$

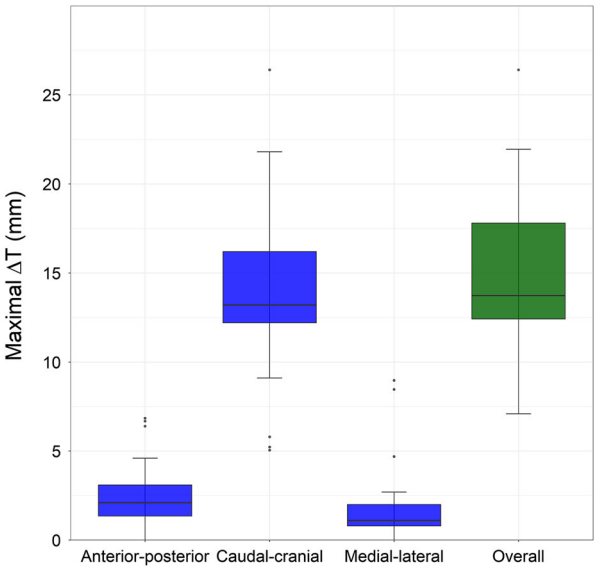


**Figure 2.** Maximal stress PET-CT translation differences ($\Delta T$) for the three directions (blue) and the derived overall translation (green) in patients with myocardial creep.

We reconstructed the two dynamic stress datasets, one with single alignment and one with frame-wise PET-CT alignment, using 3D iterative reconstruction (SharpIR) with 2 iterations and 24 subsets while correcting for decay, attenuation, scatter and random coincidences, and dead time effects. Neither time-of-flight information, nor a post-processing filter or resolution modeling was used for reconstruction.

## MBF Quantification

The reconstructed dynamic PET datasets were post-processed using Corridor4DM software (v2016). Myocardium contours were automatically detected based on the data acquired between 2:30 and 7:00 minutes. We then adjusted the myocardium contours to the observed activity for each time-frame in which myocardial creep was present. Next, a region of interest (ROI) was manually placed at the location of the mitral valve to estimate the activity in the blood pool. The activity concentrations in the myocardium contour and ROI were then measured in the 26 reconstructed time-frames to calculate the TACs for the whole myocardium and for the three vascular territories: left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA). The one-tissue compartment model of Lortie et al based on a ROI

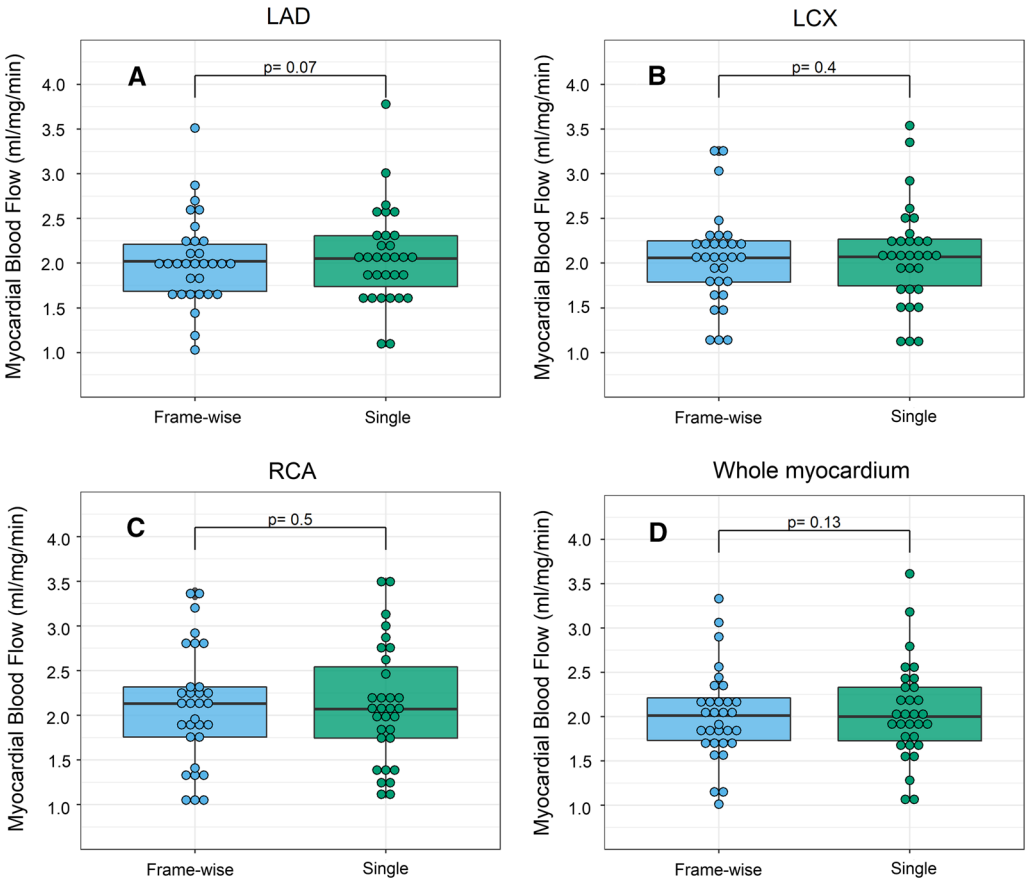


**Figure 3.** Stress myocardial blood flow (MBF, mL/min/g) for using frame-wise and single PET-CT alignment methods for the three vascular territories and for the whole myocardium. *LAD*, left anterior descending; *LCX*, left circumflex; *RCA*, right coronary artery.

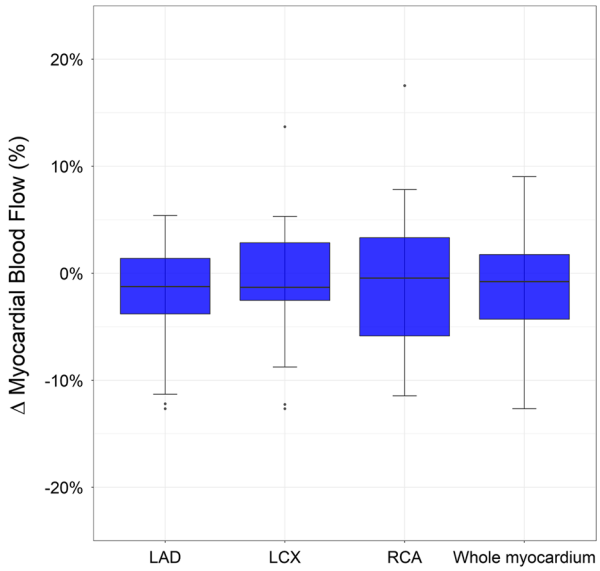


**Figure 4.** Relative difference in stress myocardial blood flow (MBF) between frame-wise and single PET-CT alignment methods for the three vascular territories and for the whole myocardium. *LAD*, left anterior descending; *LCX*, left circumflex; *RCA*, right coronary artery.

methodology was used to calculate the MBF from the TACs.[15] The MBF measurements were compared between the single and frame-wise alignment methods for all scans and were considered to result in different measurements if the standard deviation (SD) of the relative difference, defined as $(MBF_{frame\text{-}wise} - MBF_{single})/MBF_{single}$, exceeded 10%.[16]

## Statistics

Patient-specific parameters and characteristics were determined as percentage or mean ± SD using R (v3.4.1[17]). The MBF measurements based on the single and frame-wise PET-CT alignment methods were compared using the Wilcoxon signed-rank test. To determine if one of the cardiac territories or the whole myocardium showed larger MBF deviations, we compared the SD of the relative differences between the three territories and whole myocardium using the Friedman test. The correlation of the difference in MBF between the single and frame-wise AC and maximal observed translations for each vascular territory and the whole myocardium were calculated using the Pearson correlation coefficient. The level of statistical significance was set to 0.05 for all statistical analyses.

# RESULTS

## Population

Out of the 64 consecutive patients 31 (48%) showed myocardial creep during stress imaging. The baseline characteristics of these 31 patients are summarized in Table 1. Ten out of the 31 included patients showed responds in both heart frequency and systolic blood pressure after regadenoson, 20 patients showed partial response and 1 was considered a non-responder, which was presumably due to his pacemaker rhythm and anxiety. Nevertheless, as all patients showed signs of myocardial creep, we considered all patients to be stressed sufficiently.

## Myocardial Creep and PET-CT Alignment

Myocardial creep was visible in 4.3 ± 1.1 frames of the 26 time-frames. The earliest frame in which myocardial creep occurred was frame 3 (10-15 seconds post injection) and the latest was frame 12 (55-60 seconds). The maximal translation differences ($\Delta T$) between single and frame-wise alignment were 13.8 ± 4.5 mm in cranial-caudal direction (range 5.1-26.4), 1.8 ± 2.1 mm in medial-lateral direction (range 0.0-9.0), and 2.5 ± 1.8 mm in anterior-posterior direction (range 0.0-6.8), as shown in Figure 2. The maximal $\Delta T_{overall}$ was 14.8 ± 4.4 mm (range 7.1-26.4).

## MBF Quantification

The MBF measurements did not differ for any of the three vascular territories or the whole myocardium when comparing the use of frame-wise with single PET-CT alignment ($P \geq .07$), as shown in Figure 3. The largest difference in MBF was observed in the RCA territory with mean stress MBF of 2.5 ± 0.7 and 2.3 ± 0.7 mL/mg/min for single and frame-wise alignment, respectively ($P = .5$). The SD of the relative differences was 4.6% for the LAD, 5.3% for the LCX, 6.5% for the RCA and 4.7% for the whole myocardium and did not differ between the vascular territories ($P = .16$), as shown in Figure 4. As the relative differences did not exceeded 10% for any of the vascular territories, frame-wise alignment was considered to result in comparable MBF measurements. Moreover, the difference in MBF between the single and frame-wise AC did not correlate with $\Delta T$ for any of the vascular territories or whole myocardium ($P > .06$), as shown in Figure 5.

# DISCUSSION

Myocardial creep is observed in almost half of the patients undergoing regadenoson stress PET Rb-82 imaging. The resulting misalignment between the drawn myocardium contour and the true position of the myocardium in the beginning of the scan can and should be corrected in these patients during post-processing.[5] In this study, we showed that another possible source of error, the misalignment of PET-CT

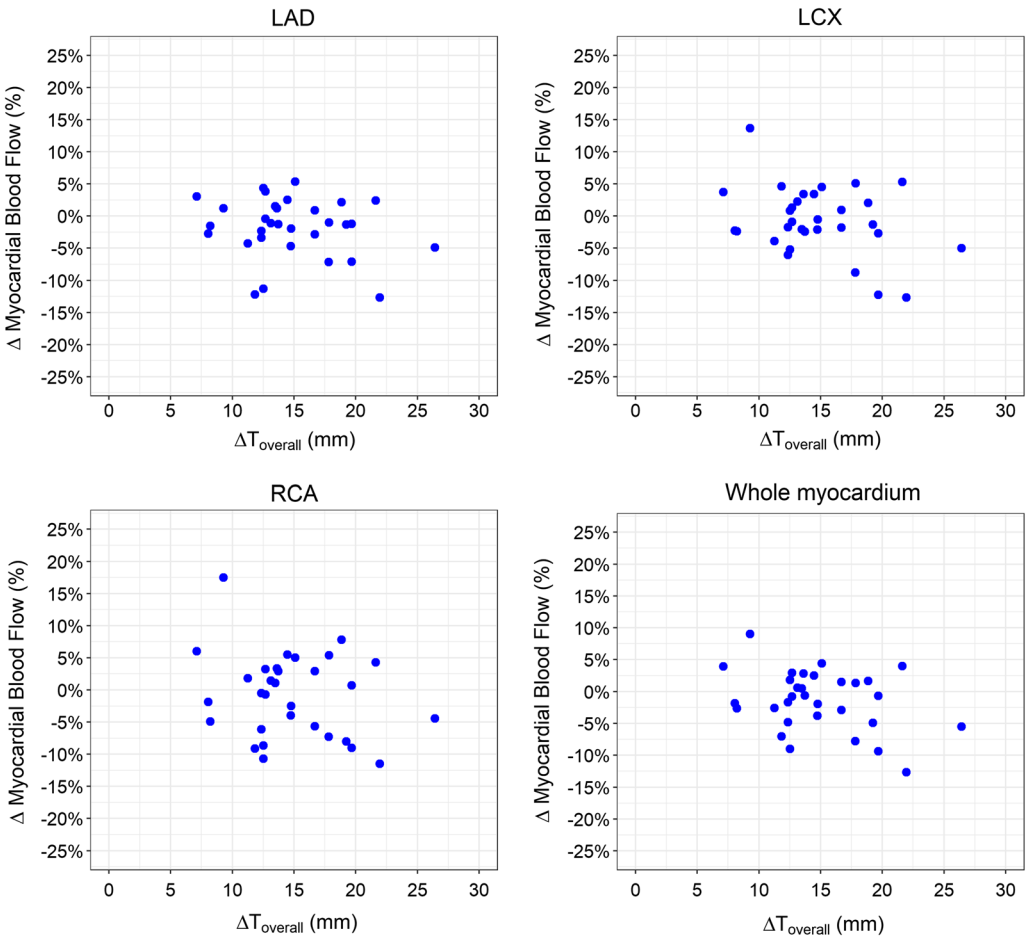


**Figure 5.** Relative difference in stress myocardial blood flow (MBF) between frame-wise and single PET-CT registration as function of $\Delta T_{overall}$ (maximal overall alignment difference) in patients with myocardial creep. All dots present individual patients.

for AC, which then still occurs, does not seem to effect the MBF values as frame-wise instead of single PET-CT alignment did not result in altered MBF measurements. Therefore, it is sufficient to correct for the misalignment (14.8 ± 4.4 mm) due to myocardial creep by adjusting the myocardium contours for each time-frame during the post-processing.

The study by Rajaram et al is the only study that reported the effect of PET-CT misalignment on MBF measurements using PET Rb-82.[12] They showed that a 10 mm PET-CT misalignment in both the lateral and caudal direction resulted in 9% higher MBFs ($P$ = .004). This is in contrast with our findings showing no significant differences in MBF in patients with a misalignment due to myocardial creep. However, they simulated an alignment error of 10 mm for all time-frames whereas in our study with authentic patient data alignment errors only occurred in the few time-frames in which myocardial creep was present. In addition, they manually misaligned the images in both the lateral and caudal direction whereas significant misalignment due to myocardial creep is generally mainly present in the cranial-caudal direction. This cranial-caudal misalignment produced fewer and smaller differences in MBF measurements, maybe due to the relatively low tissue density differences between the myocardial cavity and the myocardium tissue and in a later phase between the myocardium and gastric region as compared to the difference in tissue density between myocardium and lung tissue. As the difference in AC will then be less pronounced, it can be understood that its influence on the MBF is limited.

We made several assumptions in this study. First, we used a retrospective study design and patients were selected when myocardial creep was observed. However, as myocardial creep is absent in the excluded patients, our results would have been even less pronounced if we would have included those as well.

Therefore, we are convinced that the results hold for the entire population and can easily be generalized for all patients with myocardial creep.

Second, MBF measurements were considered to be comparable between the frame-wise and single PET-CT alignment method when the SD of the relative error did not exceeded the previously determined test-retest error of 10%.[16] Although this 10% test-retest error also includes repeating the acquisition which we did not do in this study, the maximum SD of the relative difference of 6.5% we found is well within this error range. Hence, we assume that the MBF differences between frame-wise and single PET-CT alignment were solely due to reproducibility errors.

Third, we did not use a reference standard to determine the MBF and only assessed the difference between MBF measurements using the single and frame-wise PET-CT alignment method. However, as the acquisition and MBF quantification process were identical for both alignment methods, it is safe to assume that possible differences induced by frame-wise alignment would have been visible.

Fourth, we did not assess the reproducibility of deriving the misregistration for the frame-wise AC method. The only possible variability in the used method is in the identification of the time-frames in which myocardial creep was still present. However, the presence of myocardial creep was clearly defined and possible errors would therefore only be expected in the time-frames with minor myocardial creep in which the AC-CT misregistration and effect on MBF would also be minimal. Moreover, the stress-rest scan alignment was fully automated and the selection of comparable stress and rest time-frames was purely based on the peak of the TAC which is 100% reproducible. Hence, we expect our results to be reproducible.

Fourth, we only included patients who were pharmacologically stressed using regadenoson. However, Memmot et al previously showed that myocardial creep occurs even more often when using adenosine and they suggested that it occurs for all pharmacological stress agents.[18] Moreover, myocardial creep is presumably caused by an increasing respiration and lung volume and thereby repositioning of the diaphragm and heart after induction of pharmacological stress and it seems that the direction of motion is therefore comparable for all agents.[9] Yet as the duration of myocardial creep and, hence, the number of affected time-frames might be associated with the varying duration of infusion for the different stress agents, we are unsure if our results will hold when using other pharmacological stress agents.

Finally, the low-dose CT scan was acquired using a free-breathing protocol. As the high-speed of the CT freezes heart and lungs at one phase of the respiratory cycle this can cause potential misalignment between the CT and PET data, consequently resulting in significant artifacts.[19,20] Le Meunier et al reported that this misregistration especially occurs at full-inspiration, is less often observed during shallow breathing and is minimal during end-expiration. Although we do expect that our results will hold when using an end-expiration protocol as this will presumably result in a smaller chance on misregistration, our results may not hold when using a full-inspiration protocol.

## NEW KNOWLEDGE GAINED

We demonstrated that frame-wise instead of single/general alignment of CT and dynamic PET does not influence the AC of the heart and thereby does not affect MBF measurements in patients with myocardial creep. Although a previous simulation study demonstrated that PET-CT misregistration can influence MBF quantification,[12] this was not observed in the present study in patients with myocardial creep. This is likely caused by the fact that the misalignment only occurred in the cranial-caudal direction in a few time-frames during the first minute of the acquisition in patients with myocardial creep using regadenoson. It therefore seems that the overall maximal translation difference of 14.8 ± 4.4 mm due to myocardial creep can be corrected by adjusting the myocardium contour to the activity present for the early time-frames during post-processing, and that per-frame AC is not necessary. Furthermore, as the occurrence of myocardial creep using regadenoson is expected to be independent of the used tracer, one can assume that frame-wise registration will also not be necessary when using other tracers than Rb-82.

## CONCLUSION

There is no need for frame-wise AC in dynamic Rb-82 PET for MBF quantification as it does not affect MBF quantification. General single PET-CT alignment during post-processing seems sufficient in patients with myocardial creep.

## Disclosures

*None of the authors have anything to disclose.*

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