Original article

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Minimal starting time of data reconstruction for qualitative myocardial perfusion rubidium-82 positron emission tomography imaging

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Objective **Qualitative positron emission tomography (PET) myocardial perfusion imaging (MPI) scans are reconstructed with a delay after an injection of rubidium-82 (^{82}Rb) to ensure blood pool clearance and sufficient left ventricle to myocardium contrast. Our aim was to derive the minimal starting time of data reconstruction (STDR) after an injection of ^{82}Rb for which the diagnostic value and image quality remained unaffected.**

Materials and methods **We retrospectively included 23 patients who underwent rest-stress ^{82}Rb PET MPI using 740 MBq. Patients fulfilling one of the two criteria indicating a slow blood pool clearance (ejection fraction <50% and/or cardiac output <3 l/min) were included in a consecutive manner. PET images using five different STDRs (1:15–2:15 min) were reconstructed and compared with reference images (STDR of 2:30 min). Differences in the summed rest score greater than or equal to 3 and total perfusion deficit greater than 3% were considered to significantly influence the diagnostic value. In addition, image quality was scored by two experts as not interpretable, inferior, adequate, or excellent.**

Results **The summed rest score differed greater than or equal to 3 from the reference in seven or more patients (≥30%) using STDR less than or equal to 2:00 min ($P < 0.02$). STDR less than or equal to 1:30 min resulted in six or more patients (≥26%) with a total perfusion deficit difference greater than 3% ($P < 0.03$). In addition, STDR less than or equal to 2:00 min resulted in a lower image quality ($P < 0.002$) and STDR less than or equal to 2:15 min resulted in greater than or equal to two scans with noninterpretable image quality.**

Conclusion **STDR less than or equal to 2:15 min resulted in lower diagnostic value or insufficient image quality for qualitative PET MPI using 740 MBq ^{82}Rb. An STDR of 2:30 min can be considered for clinical adoption.** ***Nucl Med Commun*** **39:533–538**

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Introduction

Despite the growing use of quantitative positron emission tomography (PET) myocardial perfusion imaging (MPI) using short half-life tracers, qualitative or visual PET assessment is still commonly used. These qualitative static images are reconstructed from a part of the list mode acquisition using a time delay, prescan delay, after tracer injection. This delay ensures blood pool or cavity activity clearance and therefore sufficient left ventricle to myocardium contrast in these static images [1]. Insufficient contrast can mask myocardial defects because of the spillover effects caused by activity in the blood pool. Although a sufficient time delay is required, an unnecessary late starting time of data reconstruction (STDR) leaves valuable data unused when using short half-life tracers such as rubidium-82 (^{82}Rb) [1].

Currently, guidelines recommend the usage of an STDR depending on heart function: 1:30–2:10 min for an ejection fraction (EF) less than 50% and 1:10–1:30 min for EF greater than 50% in ^{82}Rb PET MPI, but evidence is lacking [2,3]. Moreover, heart function is often not known before scanning. In clinical practice, we find that the activity in the blood pool is cleared after 1 min [1]. This might indicate the possibility to reduce the STDR in all patients, subsequently allowing a dose reduction because of an increase of accepted photon coincidences in the PET reconstruction. Our aim was to derive the minimal STDR for ^{82}Rb PET MPI for which the image quality and diagnostic value remained unaffected in all patients.

Materials and methods

Population

We retrospectively included all patients who underwent rest-stress MPI ^{82}Rb PET (Ingenuity TF; Philips

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Healthcare, Cleveland, Ohio, USA) within a 1-month period who had a slow blood pool clearance, indicating that a relatively late STDR is required [2]. A slow pool clearance was defined as having either an EF 50% or less [2,4] and/or cardiac output less than 3 l/min (normal range: 4–8 l/min) [5,6]. Cardiac output was calculated by multiplying heart rate with stroke volume, as determined using the PET acquisition. Twenty-three out of the 66 scanned patients fulfilled one or both criteria and were included in this study.

All patients provided written informed consent for the use of their data for research purposes. As all analyses were carried out retrospectively, no approval from the ethical committee was required according to Dutch law.

Patient preparation and acquisition

Patients were instructed not to use any caffeine containing beverages for 24 h before scanning and to discontinue dipyridamole for 48 h before scanning. Before MPI, patients underwent a low-dose computed tomography (CT) scan during free breathing to provide an attenuation map of the chest. This scan was performed using a 3 mm slice thickness, 1.5 s rotation time, a pitch of 0.825, collimation 40×0.625 mm, tube voltage of 120 kV, and a tube current that was computed automatically depending on patients' size (varying between 20 and 52 mA). For both rest and stress MPI, an ^{82}Rb activity of 740 MBq was administered at a flow of 50 ml/min (CardioGen-82; Bracco Diagnostics Inc., Princeton, New Jersey, USA) using a small volume varying between 6 and 13 ml depending on generator age. Ten minutes after the first elution, stress was pharmacologically induced with Regadenoson (400 µg in 5 ml saline over 15 s) and the activity was administered after a 10 s flush of 5 ml NaCl 0.9%. PET 3D list mode acquisition of 7 min was started at the time of injection.

Attenuation correction was applied to all data after (semi)-automatic alignment of CT and PET data. Only rest acquisitions were used in this study as the cardiac output and therefore blood pool clearance is expected to be lower during rest.

Simulating different starting time of data reconstruction delays

The reference STDR was 2:30 min after the start of injection and these scans were reconstructed till 7:00 min [7,8]. To derive the minimal STDR, we simulated the use of different STDR (t_{start}): 1:15, 1:30, 1:45, 2:00, and 2:15, which were based on the current ranges in international guidelines [2,3]. To minimize the influence of the increasing number of accepted photon coincidences when using shorter STDR, we altered the end time, t_{end}, to include a similar amount of coincidences as in the reference acquisition in each modified scan, as shown in Fig. 1. The corresponding end times of the STDR modified scans were therefore calculated using Eqn (1):

$$t_{end} = \frac{\ln\left(e^{-\lambda \cdot t_{start}} - e^{-\lambda \cdot t_{start\_ref}} + e^{-\lambda \cdot t_{end\_ref}}\right)}{-\lambda} \quad (1)$$

where $\lambda = \ln(2)/T_{1/2}$, $T_{1/2}$ representing the half-life of ^{82}Rb (76 s), t_{start_ref} the reference starting time of 2:30 min, and t_{end_ref} the end time of 7:00 min for the reference reconstruction. Hence, the five modified scans were reconstructed from 1:15–2:23, 1:30–2:53, 1:45–3:28, 2:00–4:11, and 2:15–5:11 min for each patient, further referred by modified-STDR scans.

Next, all reconstructions were postprocessed using the AutoQUANT Cardiac Suite (v2013.2; Cedars-Sinai Medical Centre, Los Angeles, California, USA). The reference acquisition was processed a second time to derive possible reproducibility errors, further referred by the reproducibility scan. Summed rest scores (SRS) and total perfusion deficit (TPD) were calculated automatically for all scans. TPD was defined as the percentage of segments below the predefined uniform average deviation threshold, as explained in detail by Berman *et al.* [9]. Scans were displayed in the traditional short, vertical long, and horizontal long axes and reviewed using the 'Cool' color scale.

Analysis

The SRS and TPD were compared between the reference and the other six scans. An SRS difference greater than or equal to 3 or TPD differences greater than 3% were considered to result in a change in the diagnostic outcome [10]. The modified-STDR scans were excluded from further analysis when, at first glance, they showed an inferior image quality in combination with clear deformation of the myocardium altering the diagnostic outcome. In the qualitative analysis, the image quality of the eligible simulations was scored by two experts by consensus using a four-point scale: (a) not interpretable, (b) inferior but interpretable, (c) adequate, and (d) excellent. Moreover, the experts jointly interpreted all scans as normal or as containing defects. All images were presented in random order, and patient characteristics and type of simulation were masked.

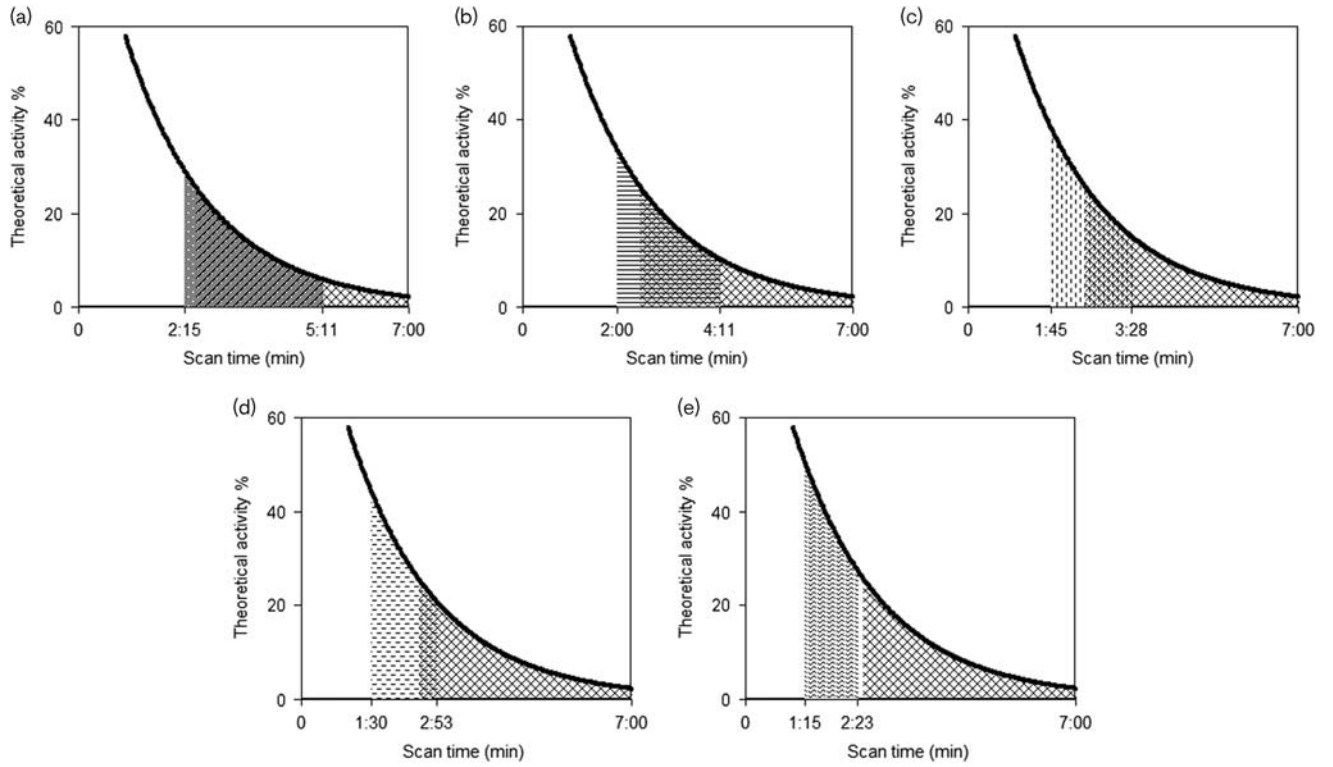
Statistics

Patient variables were computed as mean ± SD or as percentage using Stata (StataSE, version 12.0, StataCorp, College Station, Texas, USA). The number of scans with a difference of SRS greater than 3 or TPD greater than 3% was compared for each STDR simulation with the number of deviating scan using the reproducibility scan using the McNemar test. The image quality of the modified scans was compared with the reference scan using the Wilcoxon signed rank test. The level of statistical significance was set at 0.05.

Results

The baseline characteristics of all included patients are summarized in Table 1. Of the 23 patients included, nine

Fig. 1



Line graphs showing the theoretical activity of rubidium-82 as a function of scan time. The start and corresponding end times for the different starting times of data reconstructions are shown with (a) 2:15, (b) 2.00, (c) 1:45, (d) 1:30, and (e) 1:15 min. The sizes of the shaded areas, representing the amount of photon coincidences, are the same for all reconstructions including the reference scan (2:30 till 7:00 min), which is shown as the black crossed area in each subfigure.

Table 1 Baseline characteristics and scan outcomes of all 23 patients who underwent clinically indicated positron emission tomography myocardial perfusion imaging

Characteristics	
Age (years)	71 ± 10
Male sex (%)	52
Body weight (kg)	79 ± 15
Height (cm)	169 ± 11
BMI (kg/m^2)	27 ± 4
Normal MPI scan	57
Reversible defect on MPI	22
Nonreversible defect on MPI	30
Ejection fraction	60 ± 14
Cardiac output (l)	3.1 ± 1.0

Data are presented as mean ± SD or percentages.
MPI, myocardial perfusion imaging.

(39%) had an EF less than or equal to 50% and 15 (65%) had a cardiac output less than 3 l/min.

Shorter STDR resulted in more scans with a difference in SRS greater than 3 in comparison with the reference scan, as shown in Table 2. The number of deviating scans was seven (30%) using an STDR of 2:00 min, 10 (43%) using an STDR of 1:45 min, seven (30%) using an STDR of 1:30 min, and seven (30%) using an STDR of 1:15 min and all differed from the reproducibility scans ($P < 0.02$). Using an STDR of 2:15 resulted in three (13%) deviating scans in comparison with the reference scans ($P = 0.25$), whereas no reproducibility scans showed a deviation. The number of scans with differences in TPD greater than 3% also increased for shorter STDR. The number of deviating scans was three (13%) when using an STDR of 2.00 min, four (17%) using 1:45 min, six (26%) using 1:30 min, and eight (35%) when using an STDR of 1:15 min. Using an STDR of 1:30 min or less resulted in more scans with deviating TPD in comparison with the reproducibility scan ($P < 0.03$).

The STDR simulation of 1:15 was excluded for the qualitative analysis because of its inferior performance in the semiquantitative analysis and its inferior image quality and clear deformation of images, resulting in changes in diagnostic outcomes at first glance. Next, the qualitative analysis showed that the image quality decreased for shorter STDR, as shown in Figs 2–4. Image quality did differ from the reference scan for STDR less than or equal to 2:00 ($P \leq 0.011$). However, noninterpretable images were already present from an STDR of 2:15 and shorter.

The number of scans interpreted as having defects varied between the reference and the STDR simulations.

Table 2 The number of scans for each starting time of data reconstruction in which the summed rest score differed greater than or equal to 3 or the total perfusion deficit differed greater than 3 in comparison with the reference scan

	Reproducibility	2:15 [*n* (%)]	2:00 [*n* (%)]	1:45 [*n* (%)]	1:30 [*n* (%)]	1:15 [*n* (%)]
SRS ≥ 3	0	3 (13)	7 (30)*	10 (43)**	7 (30)*	7 (30)*
TPD > 3% point	0	0	3 (13)	4 (17)	6 (26)*	8 (35)**

SRS, summed rest score; TPD, total perfusion deficit.
*$P < 0.05$.
**$P < 0.01$.

Fig. 2

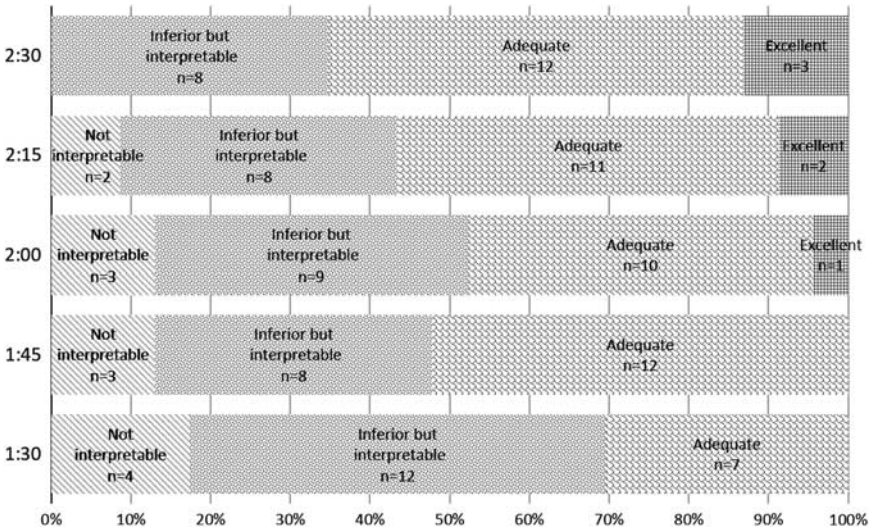


Image quality scored by two experts by consensus of the scans reconstructed using different times of data reconstructions varying from 2:30 (reference) to 1:30. Image quality differed from the reference scan for starting times of data reconstructions less than or equal to 2:00 ($P \leq 0.01$).

The number of scans with a deviating defect interpretation in comparison with the reference was three (13%) for an STDR of 2:15, two (9%) for an STDR of 2:00 min, five (22%) for an STDR of 1:45 min, and four (17%) for an STDR of 1:30 min, as shown in Fig. 2. The diagnostic interpretation changed in these scans either from normal to having small defects or from having small defects to normal using lower STDR.

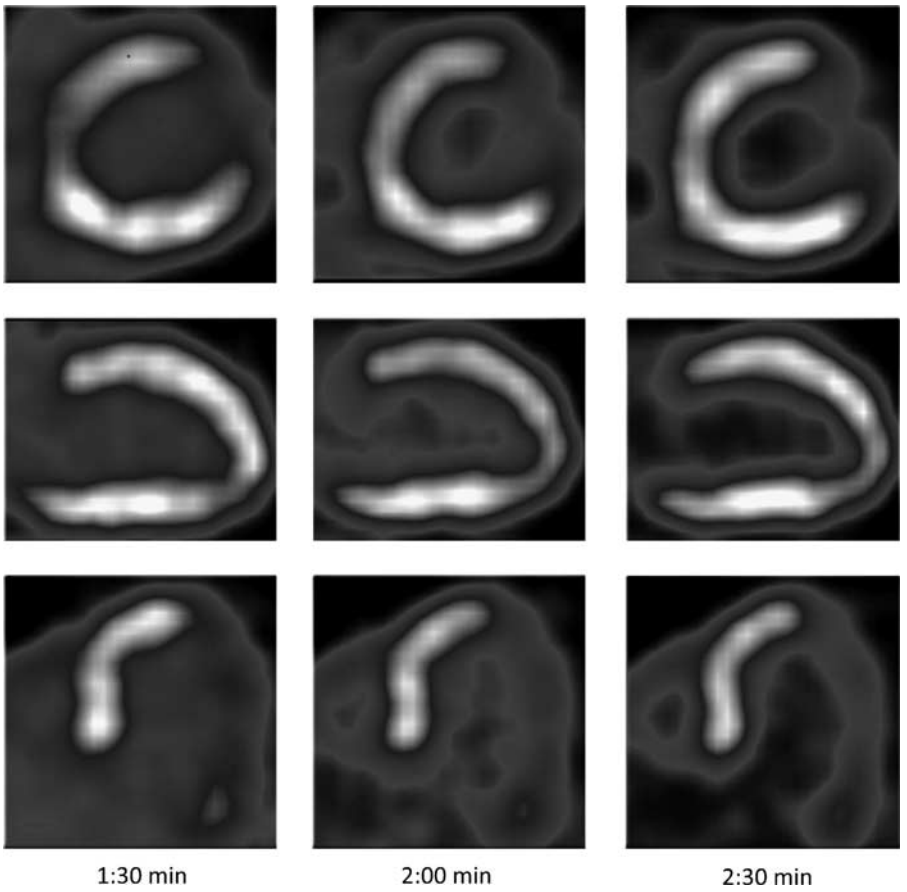
Discussion

In this study, we have shown that an STDR after 740 MBq ^{82}Rb administration may adversely affect image quality or diagnostic value when it is lower than 2:30 min. Although scans with an STDR of 2:15 did not differ from the reference delay, noninterpretable scans arose using this shorter delay, possibly indicating its inferiority.

The minimal STDR from the start of injection as derived in this study is still longer than the 1:10–2:10 min STDR range after injection that is currently recommended by international guidelines [3,11]. However, evidence supporting these recommendations is lacking and this topic appears to have been explored insufficiently. Tang *et al.* [1] carried out a modeling study on five healthy patients to predict defect detection for changing STDR. They defined the STDR as the time at which the myocardial activity became higher than the activity in the blood pool. In this way, Tang *et al.* [1] found an optimal STDR of 1:15 for rest and 1:06 min for stress MPI. These findings are in contrast to the 2:30 min as derived in the present study. Yet, they did not validate or check their protocol in patients, did not look at diagnostic outcomes, and they also did not consider image quality. Moreover, they did not take into account variation in blood pool clearance or masking of existing perfusion deficits that occurred in four (17%) of our patients using STDR of 1:30 min.

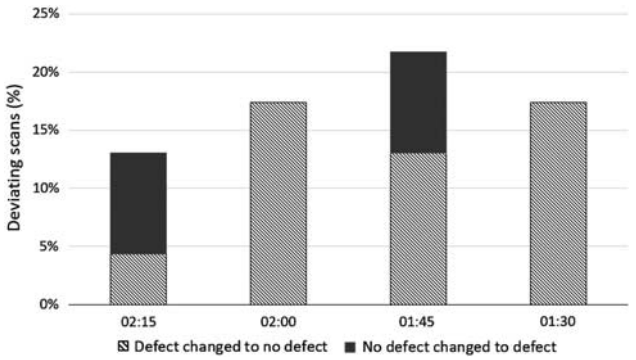
We made several assumptions in this study. First, we used a retrospective study design and patients were included if they fulfilled one of the two inclusion criteria indicating a slow blood pool clearance. These inclusion criteria ensured suitability for the majority of patients. Although the limited number of patients may have altered the results, we ensured with our inclusion criteria that all possible patients with a slow blood pool clearance were included. Although the results should be interpreted with caution because of

Fig. 3



Example of the image quality of a rest positron emission tomography myocardial perfusion imaging scan using various times of data reconstructions. Scans are from a 66-year-old female patient (84 kg, BMI of 36 kg/m^2, and ejection fraction of 48%). The 1:30 min scan was scored as poor, the 2:00 min scan as good, and the 2:30 scan as excellent. Shown from top to bottom are the corresponding short-axis slice, vertical long-axis slice, and horizontal long-axis slice. For all axes, the same locations are shown for each starting time of data reconstructions.

Fig. 4



Bar chart showing the percentage of scans with a change in defect interpretation for the modified time of data reconstruction (STDR) scans in comparison with the reference scan (2:30 min). The dashed part of the bar represents the scans in which a myocardial defect was no longer observed when using shorter STDR. The solid part represents the scans that were interpreted to not have defects but showed defects using shorter STDR.

the limited number of patients, it does indicate that an STDR shorter than 2:15 can negatively impact the scan quality. Second, we used variable end times in the simulation of the different STDR to ensure a comparable amount of accepted photon coincidences compared with the reference scan. Yet, the myocardium to blood pool activity ratio increases during acquisition. The accepted photon coincidences measured in a later stage therefore make a higher contribution toward the scan quality than photon coincidence measures in an earlier stage, which could have negatively influenced the quality of the shorter STDR scans. However, as an impaired image quality was already found at an STDR of 2:15 min, we expect this influence to be small. Third, we assumed that possible washout effects of the tracer from the myocardial tissue were minimal. Washout effects mainly occur in myocardial infarcted areas, which would enhance these areas using longer STDR [12,13]. However, washout rates of ^{82}Rb are relatively low, limiting this influence. Fourth, a relatively low ^{82}Rb activity was used in this study [14]. One could

hypothesize that a higher activity may result in sufficient image quality using an STDR of 2:15 min. Yet, a higher activity will automatically increase the administered elution volume and time, resulting in a slower blood pool clearance. As the speed of blood pool clearance mainly determines the STDR, a higher image quality is expected to be compromised by the longer elution administration time. Fifth, only rest images were used in this study. As the cardiac output and therefore blood pool clearance are expected to be lower during rest, we assumed that if the rest images were of sufficient quality, the corresponding STDR would also hold for the stress images. Finally, we considered a TPD difference of greater than 3% instead of the standard greater than 7% as a change in diagnostic outcome [9,15]. We decided to use a more sensitive TPD threshold as we observed small changes in perfusion defects when the TPD differences were less than 7% in previous studies using single-photon emission CT and PET MPI [16]. Nevertheless, the SRS still seemed more sensitive in the detection of a change in perfusion defects than TPD as shown in Table 2.

This study has an important clinical implication. The recommended STDR in international guidelines for patients with an EF less than 50% or unknown EF currently ranges between 1:50 and 2:10 min after injection. However, we showed that an STDR of 2:30 from the start of injection could result in better image quality and may positively affect defect interpretation using 740 MBq ^{82}Rb PET MPI. These results cannot be extrapolated to other PET MPI tracers used for qualitative imaging such as Ammonia-13 or Flurpiridaz-18. Because of the different extraction fractions but also the longer half-life times, other protocols should be applied for these tracers.

Conclusion

Reconstruction time delays of 2:15 min or lower resulted in a lower diagnostic value or insufficient image quality for qualitative PET MPI using 740 MBq ^{82}Rb. Yet, a delay of 2:30 min produced a sufficient image quality in all patients and can therefore be considered for clinical adoption.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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