Minimizing rubidium-82 tracer activity for relative PET myocardial perfusion imaging

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Objectives Recommended rubidium-82 activities for relative myocardial perfusion imaging (MPI) using present-generation PET scanners may be unnecessarily high. Our aim was to derive the minimum activity for a reliable relative PET MPI assessment.

Materials and methods We analyzed 140 scans from 28 consecutive patients who underwent rest-stress MPI-PET (Ingenuity TF). Scans of 852, 682, 511, and 341 MBq were simulated from list-mode data and compared with a reference scan using 1023 MBq. Differences in the summed rest score, total perfusion deficit, and image quality were obtained between the reference and each of the simulated rest scans. Combined stress-rest scans obtained at a selected activity of 682 MBq were diagnostically interpreted by experts and outcome was compared with the reference scan interpretation.

Results Differences in summed rest score more than or equal to 3 were found using 682, 511, and 341 MBq in two (7%), four (14%), and five (18%) patients, respectively. Differences in total perfusion deficit more than 7% were only found at 341 MBq in one patient. Image quality deteriorated significantly only for the 341 MBq scans ($P < 0.001$). Interpretation of stress-rest scans did not differ between 682 and 1023 MBq scans.

Conclusion A significant reduction in administered Rb-82 activity is feasible in relative MPI. An activity of 682 MBq resulted in reliable diagnostic outcomes and image quality, and can therefore be considered for clinical adoption. *Nucl Med Commun* 38:708–714 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Introduction

The use of PET with computed tomography (PET/CT) for myocardial perfusion imaging (MPI) is increasing [1,2]. This increase is not only because of better temporal resolution of PET compared with SPECT but also because of the increased availability of PET/CT systems and the introduction of strontium-82/rubidium-82 (Sr-82/Rb-82) generators [3–5]. These generators introduced the possibility of performing PET MPI without the need for a cyclotron, as is required when using nitrogen-13 ammonia or oxygen-15 water.

PET MPI can be evaluated in two ways: relatively, by assessing the amount of activity for each myocardial region relatively to the perfusion in the rest of the myocardium, or quantitatively, by assessing the absolute myocardial blood flow in the coronary arteries [6]. Ideally, both evaluations complement each other and can be created from one acquisition [7]. Although relative perfusion requires a minimum activity to result in images with enough count statistics, quantitative perfusion is limited by a maximum activity up to which count statistics are reliable enough for flow calculations [8]. This is related to dead time effects of the PET scanner [7]. It is therefore crucial to identify an activity that is both high enough for reliable relative interpretation and low enough to limit dead time effects influencing quantification.

Several approaches for reducing the activity required for relative PET MPI have been studied, including weight-specific protocols [9], stress-only MP [10], hardware advances, and new reconstruction protocols [11]. However, the Rb-82 activity that is generally administered is still in the same range as the activities used in the first studies in the 1980s and 1990s [12–15], even though scanning equipment has improved [15]. Both American and European guidelines still recommend activities of 1110–1480 MBq for three-dimensional lutetium yttrium orthosilicate systems [16,17]. Dilsizian *et al.* [15] already suggest that with advances in PET instrumentation, lower activities, starting from 740 MBq, may be sufficient for accurate MPI, but studies confirming this are lacking [6]. Hence, our aim was to derive the minimum required

Rb-82 activity to administer that enables a reliable relative MPI assessment.

Materials and methods

Study population

We retrospectively included 28 consecutive patients with suspected coronary artery disease who were referred to our hospital for rest-stress MPI using PET/CT (Ingenuity TF PET/CT; Philips Healthcare, Cleveland, Ohio, USA). Analyses were carried out retrospectively and no approval from the medical ethical committee was therefore required according to Dutch law. Nevertheless, all patients provided written informed consent for the use of their data for research purposes.

Patient preparation and acquisition

Patients were asked to abstain from any caffeine-containing food or drink 24 h before scanning and to discontinue dipyridamole for 48 h. Before MPI, patients underwent a low-dose CT scan during free breathing to provide an attenuation map of the chest. This scan was performed using a 3 mm slice thickness, a 1.5 s rotation time, a pitch of 0.825, collimation 40×0.625 mm, a tube voltage of 120 kV, a tube current of 38–87 mA, automatically computed depending on the patient's size, and a dose length product of 99 ± 22 mGy cm. For the MPI rest scan, an activity of 1023 MBq Rb-82 was administered at a flow of 50 ml/min (CardioGen-82; Bracco Diagnostics Inc., Princeton, New Jersey, USA). Ten minutes after the first elution, stress was pharmacologically induced with regadenoson (400 µg in 5 ml saline over 15 s). After a 10 s flush with saline, again 1023 MBq Rb-82 was administered. PET list-mode acquisitions of 7 min were acquired following both Rb-82 administrations. We reconstructed the relative perfusion images using data acquired between 2:30 and 7:00 min after the start of acquisition. The low-dose CT scan was used for attenuation correction. Default PET reconstruction settings were used as recommended by the manufacturer: three-dimensional ordered-subset iterative time-of-flight (TOF) blob-based reconstruction. The radiation dose was calculated using an effective dose conversion factor of 0.8 mSv/GBq for Rb-82 and a thorax conversion factor of 0.017 mSv/mGy/cm for the CT-scans [18,19].

Simulating lower activities

We used list-mode data from the rest and stress scans to simulate the use of lower activities: 852 MBq (17% reduction), 682 MBq (33% reduction), 511 MBq (50% reduction), and 341 MBq (67% reduction). Simulations were created by starting the reconstruction of list-mode data later than the reference of 2:30 min while keeping the end time at 7:00 min. This delay was proportional to the expected loss in counts when using lower activities. The reconstruction times as used are listed in Table 1.

**Table 1** Reconstruction times used to simulate lower activities

Activity (MBq)	Reconstruction times (min)
1023 (reference scan)	2:30–7:00
852	2:48–7:00
682	3:10–7:00
511	3:37–7:00
341	4:13–7:00

The reference scan and the four simulated lower activity scans were postprocessed using AutoQUANT Cardiac Suite (Cedars-Sinai Medical Centre v2013.2, Los Angeles, California, USA). The scans were displayed in the traditional short, vertical long and horizontal long axes and in a 17-segment bullseye representation with segmental uptake values normalized to the highest pixel value, as shown in Fig. 1. To assess the influence of reproducibility errors from the manual component of postprocessing, the reference scan with reconstruction time 2:30–7:00 min representing 1023 MBq was postprocessed a second time by the same operator in AutoQUANT. This resulted in a second reference scan, further referred to as the reproducibility scan. The reproducibility scan was used to assess the intraoperator variability of the manual component of postprocessing. Segmental uptake values, reversibility scores, summed stress scores, summed rest scores (SRS), summed difference scores (SDS), and total perfusion deficit (TPD) were automatically derived [20].

Analysis

In the first part of this analysis, we determined the lowest activity for which the segmental uptake values, SDS, and TPD did not differ statistically significantly from the reproducibility scan and could be considered eligible for clinical adoption. Rest scans were used as they are expected to be the most sensitive in showing changes when lowering the activity because of the lower myocardial activity uptake compared with stress. First, we compared the semiquantitative outcomes: TPD, SRS, and segmental uptake values between the reference and both the reproducibility and simulated low-activity scans. Differences in TPD more than 7% [21,22], SRS of at least 3 [23], and absolute segmental uptake value differences of at least 5% point were considered to possibly influence diagnostic outcome [21,24,25]. For the qualitative analysis, two expert readers separately scored the image quality of the reference scan and simulated scans, with arbitration of a third expert in case of discordance. The image quality was scored as inferior or adequate to produce an accurate clinical diagnosis. All readers were blinded to patient characteristics and activities, and images were presented in a random order. In addition, the influence of BMI on the image quality for all scans was assessed by comparing the image quality between different BMI categories (BMI < 25 kg/m^2, BMI 25–30 kg/m^2, and BMI > 30 kg/m^2 [26]).

Fig. 1
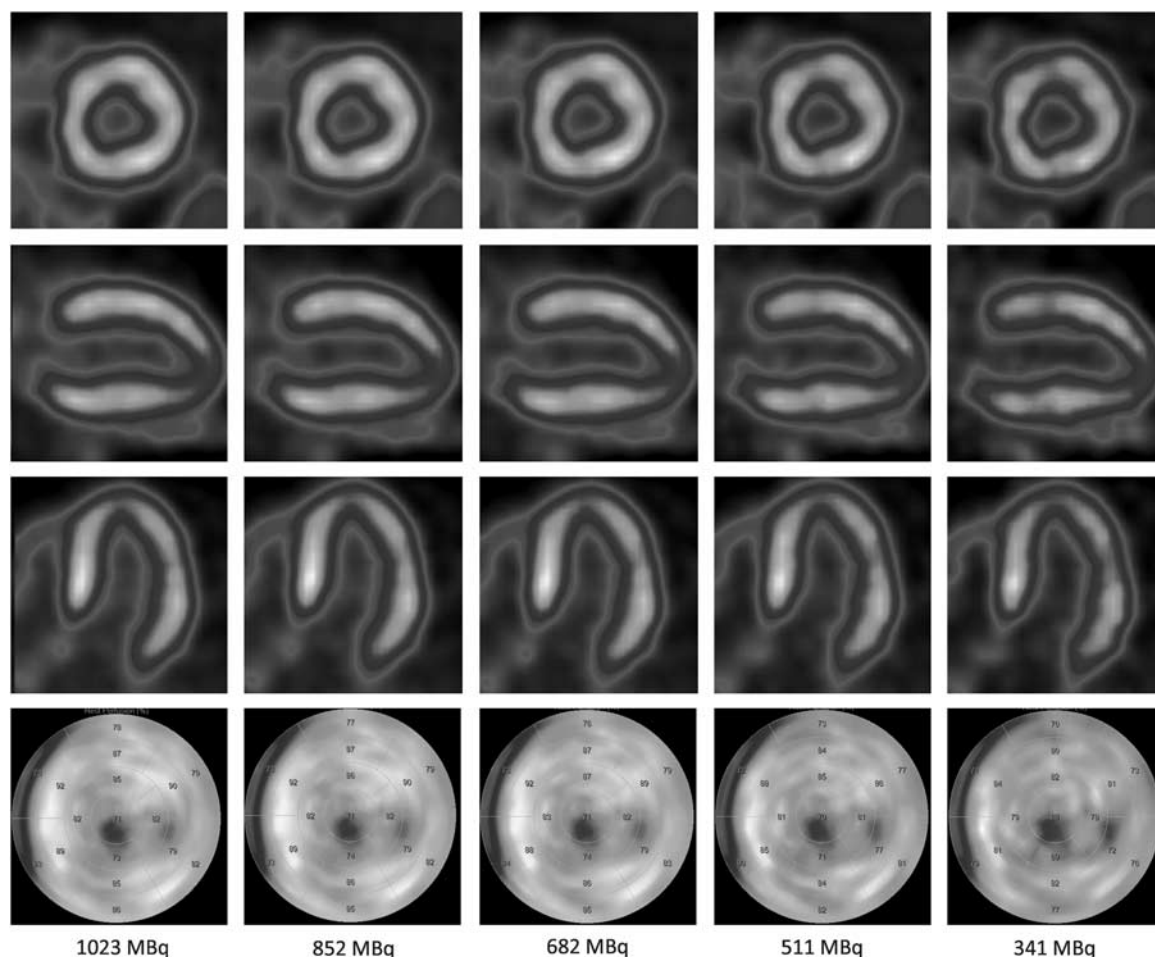
Example of Rb-82 activity rest simulations in PET/CT myocardial perfusion imaging of an 86-year-old woman (95 kg, BMI 33.7 kg/m^2). Shown from top to bottom are a short axis slice, a vertical long axis slice, a horizontal long axis slice, and a polar plot. Image quality was scored as adequate, except at 341 MBq, where it was considered inferior. CT, computed tomography; Rb-82, rubidium-82.

To ensure its eligibility for clinical adaptation, we carried out a second more in-depth analysis using the simulated activity at which the diagnostic outcome did not significantly differ from that of the reference scan. Both stress and rest images of this simulated activity were compared with the reference scan, considering three semiquantitative parameters. These parameters consisted of TPD for both rest and stress images, the SDS, and the reversibility scores, also known as segmental difference scores. The reversibility scores were based on a pixel-by-pixel comparison of the uptake values during the stress and rest scans. For the second qualitative analysis, stress and rest images of the reference and simulated activities were assessed together by two expert readers reaching consensus. Images were interpreted as normal or containing reversible and/or irreversible defects. In case of defects, the size (small, medium, or large) and location (anterior, inferior, lateral, posterior, septal, and/or apical) were assessed. The readers were blinded to patient characteristics and activity, and the images were presented in a random order. The interpretations of the scans were compared between the simulated and the reference activity.

Statistics

Patient characteristics were computed as mean ± SD or percentage of total using SPSS Statistics 22.0 (IBM Corporation, Armonk, New York, USA). The differences in SRS, TPD, segmental uptake values, and image quality between the reproducibility scan and the simulated lower activity scans were compared using the Wilcoxon signed-rank test and the McNemar test. The image quality between the different BMI categories was compared using the χ^2-test. The level of statistical significance was set at 0.05.

Results

Patient characteristics and the scan outcomes of all the patients included are summarized in Table 2.

Analysis

The number of patients in whom SRS differed by at least 3 from the reference scans increased with lower injected activities from two (7%, $P = 0.50$) using the 682 MBq simulated scans to four (14%, $P = 0.13$) using the 511 MBq scans and to five (18%, $P = 0.06$) using the 341 MBq simulated scans. We did not encounter any cases with an SRS difference of at least 3 comparing the reference with the reproducibility or 852 MBq simulated scans. Changes of more than 7% in TPD only occurred in one scan when comparing the reference with the simulated scan of 341 MBq.

We found a segmental change of at least 5% in three scans comparing the reference with the reproducibility or 852 MBq scan. At lower activity simulations, the number of scans with segmental changes of at least 5% increased to six (21%), 13 (46%), and 23 (82%) using the simulated scans of 682, 511, and 341 MBq, respectively. Only the 511 and 341 MBq simulations were statistically different from the reproducibility scan ($P = 0.006$ and < 0.001, respectively). The above results are summarized in Table 3.

The image quality of rest scans did not differ between the reference scan, the reproducibility scan, and the simulated scans of 852 and 682 MBq. However, more scans were scored as having inferior quality using simulated activities of 511 or 341 MBq compared with the reproducibility scan ($P = 0.13$ and < 0.001, respectively). Results are summarized in Fig. 2. In addition, the image quality did not differ between the BMI groups for the reference or any of the simulated activities ($P > 0.41$).

On the basis of the above data, we identified the simulated activity of 682 MBq to be the lowest activity for

which the diagnostic outcome did not differ from the reference scan and, hence, this simulation was used in a second analysis using both the stress and the rest scans. The simulated stress and rest scans of 682 MBq did not differ from the reference scans when using the criteria TPD more than 7%. We encountered changes in the criteria SDS of at least 3 in two scans (SDS differences of 3 and 4) and we encountered differences in the reversibility scores of at least 5% points in six other scans (varying between one and three deviating segments) when comparing the 682 MBq with the reference scan. Image results of two patients where differences in these semiquantitative scores were observed are shown in Fig. 3. Despite these small differences in semiquantitative scores, the overall diagnostic interpretation (normal, reversible, and/or irreversible) did not change in any of the patients when using the simulated 682 MBq scans. Yet, in 14%, a small change in defect size (from small to medium or medium to large or vice versa) occurred and in one patient an additional irreversible defect was observed in the inferior wall.

Discussion

In this study, we showed that the image quality and diagnostic visual outcome did not differ significantly when we decreased the Rb-82 activity from 1023 to a simulated activity of 682 MBq in relative MPI using a state-of-the-art PET/CT system. Although simulating 682 MBq for both stress and rest scans did show small changes in SDS and reversibility scores, the diagnostic outcome remained unaffected. An activity of 682 MBq can therefore be considered for clinical adoption.

Few studies have assessed the minimum activity required for relative MPI using PET [9,27]. Hoff *et al.* [27] reported in a recent conference proceeding abstract that an activity of 341 MBq still resulted in reliable myocardial blood flow quantification on MPI-PET, but the type of scanner was not mentioned. They also reported a lower image quality for relative perfusion imaging at this low activity, but did not report the effect on the diagnostic outcome of the relative perfusion images. Their results are in agreement with our study showing a decreased image quality for relative MPI when lowering the activity to 341 MBq. Moreover, Tout *et al.* [7] reduced the administered Rb-82 activity in their study to a level at which detector block saturation in their

Table 2 Characteristics of all 28 patients with suspected coronary artery disease referred for myocardial perfusion imaging-PET imaging including the scan outcome

Characteristics	Mean ± SD
Sex (male) (%)	53.6
Age (years)	70.4 ± 10.3
BMI (kg/m^2)	28.6 ± 4.2
Weight (kg)	83.5 ± 11.5
Length (cm)	171 ± 10
Normal scan (%)	67.9
Irreversible defect (%)	17.9
Reversible defect (%)	21.4

Table 3 Percentage of the patients with differences between the reference and simulated or reproducibility scans, possibly influencing the diagnostic outcome in total perfusion deficit, summed rest score, and segmental uptake values

	1023 vs. 1023 MBq (%)	1023 vs. 852 MBq (%)	1023 vs. 682 MBq (%)	1023 vs. 511 MBq (%)	1023 vs. 341 MBq (%)
ΔTPD > 7%	0	0	0	0	4
ΔSummed rest score ≥ 3	0	0	7	14	18
ΔSegment ≥ 5% points	11	11	21	46**	82***

The asterisks indicate the result of the McNemar test comparing the simulated scans with the reproducibility scans.
**$P \leq 0.01$.
***$P \leq 0.001$

scanner (Biograph mCT PET scanner; Siemens Healthcare) was absent, which was 1110 MBq. However, they did not derive the minimum activity for adequate

Fig. 2
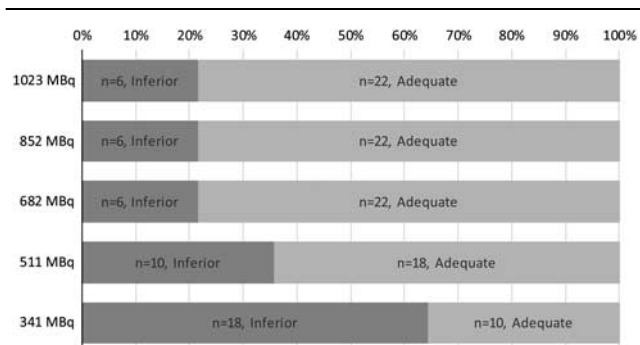
Expert reader assessment of image quality scored as inferior or adequate for the reference and four simulated scans. Image quality deteriorated significantly only for the 341 MBq scans ($P < 0.001$).

relative MPI. Finally, Renaud *et al.* [9] reported in the rubidium-ARMI trial that the image quality was scored as good or better in 76–90% of the patients when using a low-activity weight-dependent activity protocol of 10 MBq/kg Rb-82. Although the Rb-82 generator that we used (CardioGen-82; Bracco Diagnostics Inc.) cannot administer patient-specific activities [9,28–30], the minimum activity recommended for clinical adoption in our study is still 158 MBq lower for an average patient of 84 kg than in the rubidium-ARMI trial.

Several assumptions underpinned this study. First, we used a retrospective study design with a relatively small sample size. We attempted to minimize this influence by a consecutive inclusion of all patients and using paired-wise comparisons to limit the need for a large cohort. We did encounter a relatively high percentage of normal interpreted scans (68%), which could suggest that the reference activity was not sufficient for defect detection. However, this percentage was lower than the previously

Fig. 3
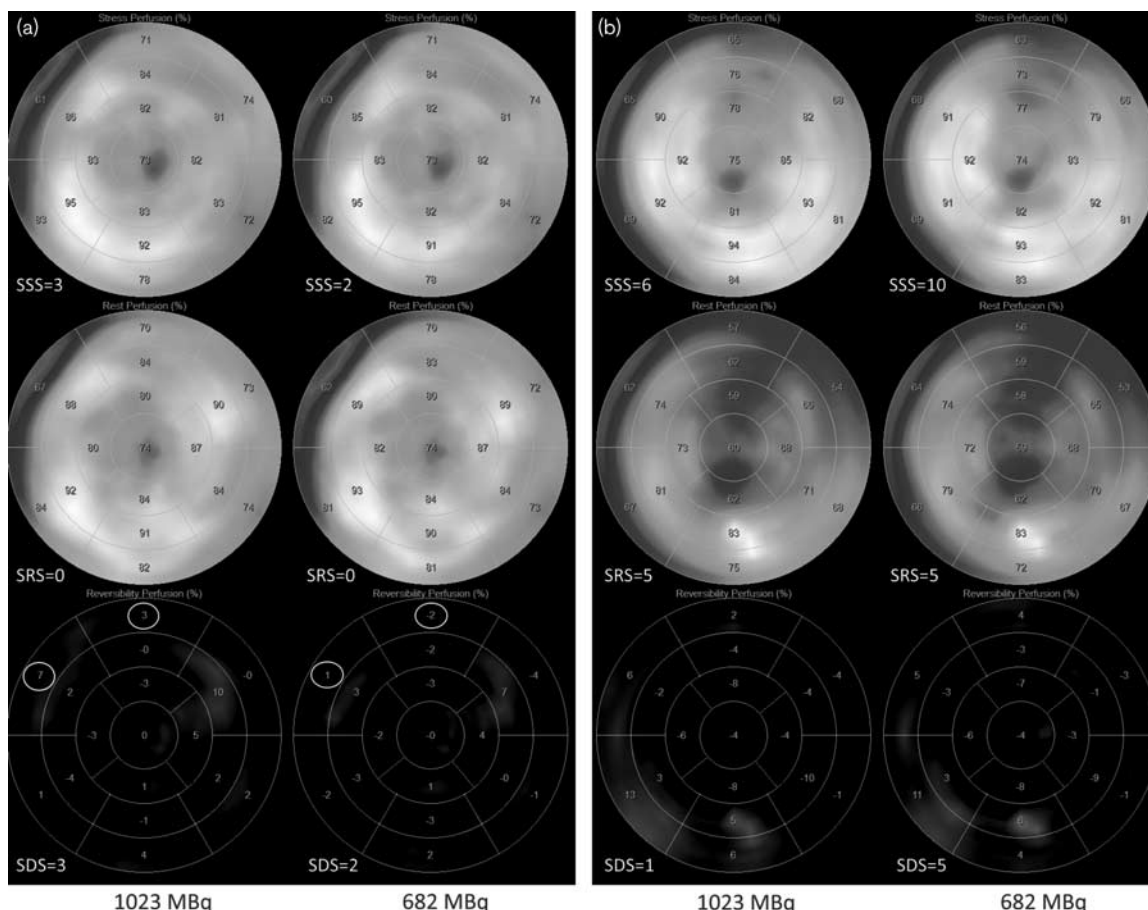
Example of two Rb-82 stress-rest scans of (a) a 69-year-old man (62 kg, BMI 20.9 kg/m^2) and (b) a 72-year-old woman (74 kg, BMI 27.5 kg/m^2) using 1023 MBq and a simulated activity of 682 Mbq. Shown from top to bottom are the stress, rest, and difference bullseye images. In scan (a), the reversibility scores differed in two segments of at least 5% points as shown in the white circles and in (b) a difference in summed difference scores (SDS) of 4 was observed. Nevertheless, the diagnostic interpretation was identical for the two scans in both patients. Rb-82, rubidium-82.

reported 76% that we encountered in a similar population referred for SPECT MPI in our hospital [31] and was therefore not considered to be because of the amount of administered activity. Second, we carried out this study solely on an Ingenuity TF PET system. The sensitivity and TOF performance of a PET system heavily influences the minimal activity required, which makes the generalizability of the presented results to other state-of-the-art PET systems difficult. However, the system sensitivity and TOF performance of the Ingenuity TF are comparable to or worse than that of other state-of-the art PET systems such as the Discovery 710 (GE Healthcare), Discovery IQ (GE Healthcare), or Biograph mCT Flow (Siemens) [32]. Hence, we may assume that our results can be adopted on these PET systems. One should be cautious when adopting the derived minimal activity on non-TOF systems or systems not using lutetium yttrium orthosilicate or lutetium oxy-orthosilicate crystals as these have a different system performance [15,33]. Third, we used a reference activity of 1023 MBq instead of 1110–1480 MBq as currently recommended by the guidelines [16,17]. This might have resulted in a lower reference image quality because of the decreased counts statistics. However, as the image quality at activities of 852 and 682 MBq did not differ from our reference scan, we can safely assume that the use of a higher activity does not result in a better image quality. In addition, the six patient scans with an inferior image quality at 1023 MBq all had extracardiac activity, obscuring the inferior myocardial wall, or had a very poor perfusion, which is not expected to be influenced by the amount of activity used. Fourth, we simulated the use of lower activities by delaying the start of the reconstruction instead of deleting a certain percentage of the measured coincidences. The data clipping method used does not account for possible tracer washout effects or the increased myocardium-to-blood contrast ratio. However, washout rates of Rb-82 are relatively low [34,35] and are expected to be limited in a reconstruction delay of maximal 40 s (682 MBq scans). Moreover, the influence of the increasing myocardium-to-blood contrast ratio, favoring the lower activity simulations, is expected to be limited [18,36]. The starting delay for the reconstructions was at least 150 s in which the myocardium-to-blood contrast ratio is already high and stabilized, minimizing this influence [3,7,17,37]. Fifth, the standard reconstruction parameters as recommended by the vendor were used. Further optimization of reconstruction parameters may improve image quality and aid image interpretation at low-activity levels, possibly enabling further reduction of the administered activity [38–40]. Finally, although the simulated scans of 682 MBq did not differ significantly from the reference scans, possible clinically important differences occurred in the reversibility scores and SDS. However, as the clinical interpretation did not change in any of the patients using the 683 MBq simulations, we expect that the changes in segmental uptake value and SDS might be too small to be visually observed or may be because of reproducibility errors.

Clinical adoption of this lower Rb-82 activity has several implications. The effective dose from a Rb-82 stress-rest MPI-PET will decrease from 1.8 with 33% to 1.2 mSv. The total effective dose, which includes the CT scan for attenuation correction, will decrease with 17% from 3.46 ± 0.36 to 2.9 mSv per study when lowering the activity from 1023 to 682 MBq. Lowering the activity also reduces count rates, which prevents detector saturation. Hence, less dead time corrections will be needed, potentially resulting in a more reliable myocardial quantification [7,18,28,29]. The PET system used in our study has a linear response rate up to a peak singles rate of 65 Mcps, corresponding to ~925 MBq [41]. This means that 682 MBq is an activity that is both high enough for reliable relative interpretation and low enough to limit dead time effects. Finally, administration of a lower activity will also reduce the elution volume required per scan. This lower elution volume can result in a longer use of specific Rb-82 generators (CardioGen-82; Bracco Diagnostics Inc.) as the maximum cumulative eluted volume of 17 l is less likely to be exceeded (*http://www.braccoimaging.com/sites/braccoimaging.com/files/technica_sheet_pdf/Cardiogen Full Prescribing Information.pdf*).

Conclusion
A significant reduction in the currently recommended Rb-82 activity by the guidelines is feasible in relative MPI using a state-of-the-art PET/CT system. An activity of 682 MBq resulted in reliable diagnostic outcomes and image quality and can therefore be considered for clinical adoption.

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