

Comparison of maximal Rubidium-82 activities for myocardial blood flow quantification between digital and conventional PET systems

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Background. PET-based myocardial blood flow (MBF) quantification can be inaccurate when using high tracer activities. Our aim was to derive the maximal Rubidium-82 activity for MBF assessment using a new digital PET system and compare the results with conventional analog systems.

Methods. 1.8 GBq Rubidium-82 was injected into the cardiac insert of an anthropomorphic torso phantom. Data were acquired for 10 min using an Ingenuity TF (Philips Healthcare), Discovery 690 (D690, GE Healthcare), and digital PET prototype system (Philips Healthcare). The dynamic ranges, defined as the maximal measured activity in the reconstructed images deviating < 10% from the true present activity, were determined in all scans.

Results. The dynamic ranges were 312 MBq for Ingenuity TF, 650 MBq for D690, and 654 MBq for digital PET prototype.

Conclusions. The maximal Rb-82 activity for MBF assessment using digital PET prototype is higher than that for its analog counterpart (Ingenuity TF), but seems comparable to the D690. (J Nucl Cardiol 2019;26:1286–91.)

Key Words: Digital PET • direct photon counting • dynamic range • cardiac positron emission tomography • rubidium-82

Abbreviations

CT	Computed tomography
COV	Coefficient of variation
MBF	Myocardial blood flow

PET	Positron emission tomography
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INTRODUCTION

Quantification of absolute myocardial blood flow (MBF) with PET myocardial perfusion imaging (MPI) is

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being increasingly used. It has been shown to provide relevant clinical information which, combined with conventional qualitative MPI, can increase diagnostic

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accuracy.^{1,2} However, the use of high activities of short-lived PET tracers can negatively influence the accuracy of the quantification of MBF.³ In particular, when dealing with high count rates, deviations between the measured and injected activities potentially make MBF quantification less reliable.⁴ Rubidium-82 has a relatively short half-life of 76 s, and high activities are therefore required to obtain sufficient image quality. A new PET system with digital photon counting technology using silicon photomultipliers may be more suitable for MBF quantification with Rubidium-82. This digital PET system has an increased temporal and spatial resolution, but its count-rate performance at high activities is still unknown.^{5,6} Our aim was to derive the maximal Rubidium-82 (Rb-82) activity that can be used for MBF quantification using a research digital PET prototype system and compare the results with two commercially available conventional analog state-of-the-art PET systems.

METHODS

Image Acquisition and Reconstruction

The methodology used in this study is based on the recent study by Renaud et al. who introduced a method to derive the quantitative MBF operating range for a PET system.⁴ In short, we injected a maximal bolus of Rb-82 activity (CardioGen-82, Bracco Diagnostics Inc.) into the cardiac insert of an anthropomorphic torso phantom (model ECT/TOR/P, Data Spectrum Corp.) so that at least 1.8 GBq Rb-82 was present at the end of infusion. The phantom was scanned in prone position in the field of view of the 3D PET scanner, and the 10-min list-mode acquisition was started at the end of infusion. Acquisition was immediately followed by a CT-scan for attenuation correction purposes. Data were acquired on two analog systems: Ingenuity TF (Philips Healthcare) and Discovery 690 (D690, GE Healthcare); and on a research digital PET prototype system^{5–7} (Philips Healthcare).

All three datasets were reconstructed into dynamic images containing 40 frames of 15 s each, using vendor-recommended iterative expectation maximization reconstruction settings. Default clinical corrections for attenuation, scatter, randoms, detector efficiency, dead-time effects, and decay were applied.

Quantitative Analysis

The reconstructions were loaded into IntelliSpacePortal (ISP 7.0, Philips Healthcare). Next, we drew a spherical volume-of-interest encapsulating the cardiac insert and measured the activity concentration in each time frame, as previously shown by Renaud et al.⁴ The difference in measured decay-corrected activities between two time frames became less than 1% after frame 24 (345–360 s after start injection) in all scans. To account for possible calibration errors, the ratio between the mean measured activity in frames 24–26 and the true present activity at these time points were calculated for all three scans. We corrected the activity

measurements for each scan with its corresponding ratio. Next, the activity bias was calculated for each time frame (t) using the following formula:

$$\text{Activity bias}(t) = \left(\frac{\text{measured activity}(t)}{\text{true present activity}(t)} - 1 \right) \times 100\% \quad (1)$$

with the true present activity defined as

$$\text{True present activity}(t) = \text{true activity}(t=0) \times e^{-\lambda t} \quad (2)$$

where λ is the decay constant of Rubidium-82: $\ln(2)/1.27 \text{ min}^{-1}$. For each scanner, the dynamic range was determined as the maximal measured activity for which the activity bias was 10% using linear interpolation between measured activities.⁴ Further, the activity bias and death time factors derived from the image headers were explored as function of the true present activity, and the maximal measurable activity was determined for each of the systems.

Image quality was assessed by deriving the nonuniformity of the activity distribution in the polar plots. of the cardiac insert. First, we determined the activity concentration per segment (Corridor4DM, v2015.02.64, Invia). Next, we calculated the coefficient of variation (COV) of the polar map:

$$\text{COV}(t) = [A]_{\text{sd}}(t) / [A]_{\text{mean}}(t) \times 100(\%) \quad (3)$$

with $[A]_{\text{mean}}$ being the mean activity concentration over all segments and $[A]_{\text{sd}}$ the standard deviation of the activity concentrations over the 17 segments.

RESULTS

The absolute activity bias increased for all three scanners with the increasing activity, as shown in Figure 1A. The dynamic range was 312 MBq for the Ingenuity TF, 650 MBq for the D690, and 654 MBq for the digital PET prototype system. When solely looking at the activity bias for each scanner for different activities, we see that the D690 and digital PET prototype were comparable in the activity range lower than approximately 900 MBq. However, when activity increases, the activity bias of the D690 became larger in comparison to that of the digital PET prototype, as shown in Figure 1B. The dead-time factors of both analog PET systems were higher for all activities in comparison to those of the digital PET prototype, as shown in Figure 1C. The dead-time corrections were 1.6 for the Ingenuity TF, 1.5 for the D690, and 1.1 for the digital PET prototype at their corresponding dynamic ranges, as shown in Table 1. Moreover, the maximal measurable activity was 471 MBq for the Ingenuity TF, 915 MBq for the D690, and > 1295 MBq for the digital PET prototype.

The nonuniformity of the cardiac insert of the phantom was stable for all scanners for activities up to 1400 MBq, as shown in Figure 1D. These results

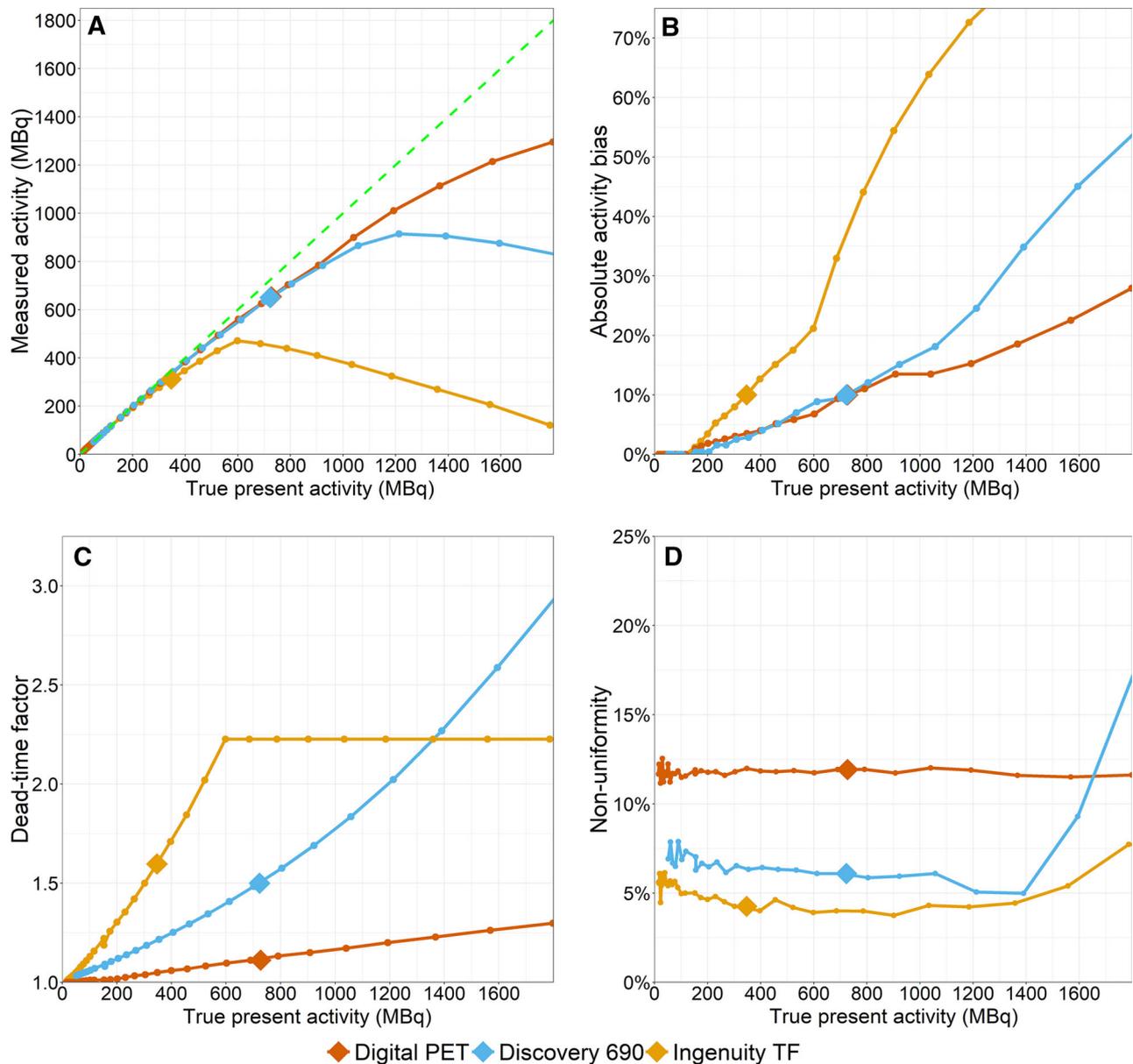


Figure 1. Line graph showing **A** the measured activity, **B** the absolute activity bias, **C** the dead-time factor, and **D** the nonuniformity as a function of the true present Rb-82 activity in the cardiac insert of the anthropomorphic torso phantom. The solid lines represent the Ingenuity TF (orange), D690 (blue), and digital (red) PET results. The diamonds indicate the dynamic ranges and the green dotted line in **A** represents the line of identity.

suggest that despite the high dead-time losses at higher activities, the image quality is not compromised.

DISCUSSION

The count-rate performance of the three PET scanners differed in dynamic range, dead-time factor, and maximal measurable activity. The D690 and digital PET prototype outperformed the Ingenuity TF in both dynamic range and detectable maximal Rb-82 activity.

Although the activity bias increased for all scanners using activities exceeding the dynamic range, this effect seems to remain limited for the digital PET prototype system as the bias increased monotonically.

Comparison with Previous Studies

Two other studies previously established the dynamic range of the two analog systems that we used in our study. Kolthammer et al. determined the count-

Table 1. Performance metrics of various PET systems

PET system	Dynamic range (measured activity, MBq)	Dynamic range (true present activity, MBq)	Dead-time factor
<i>Biograph mCT PET-CT-40</i>	720	790	-
Digital PET-CT prototype-128 (Philips)	654	725	1.1
Discovery 690 PET-VCT-64	650	722	1.5
<i>Discovery 690 PET-VCT-64</i>	570	625	1.5
<i>ECAT Accel Scintron PET 2D</i>	570	625	1.7
<i>Discovery IQ (5 ring) PET-CT-16</i>	565	620	3.9
<i>Biograph TruePoint PET-CT-16</i>	400	440	-
<i>Discovery 600 PET-CT-16</i>	325	360	2.0
Ingenuity TF PET-CT-128	310	345	1.6
<i>Biograph PET-CT-16</i>	275	300	-
<i>Discovery RX PET-CT-16</i>	255	280	1.7
<i>Gemini TF PET-CT-16</i>	230	255	-
<i>Discovery STE-VCT-16</i>	195	215	2.1
<i>ECAT Accel Scintron PET 3D</i>	135	150	1.7

From left to right: the dynamic range, defined as the maximal measured activity deviating $\leq 10\%$ from the true present activity; the true present activity at this dynamic range and the dead-time factor at the dynamic range are derived from the image headers. The system results shown in bold represent data from our study, whereas the ones in italic are the results as reported by Renaud et al.⁴

rate performance of the Ingenuity TF⁸. They reported that an activity of 925 MBq still resulted in accurate MBF quantification as the measured activity increased linearly with count rate up to this activity. Their results are in contrast with the dynamic range of 312 MBq as we determined for the Ingenuity TF. Yet they used a different, cylindrical phantom, did not determine the dynamic range, and did not specify how they determined this cutoff value. They reported that the counts lost to dead-time effects increased for activities > 300 MBq but it is unclear how this corresponds with the nondeviating activity concentration measurements for activities up to 925 MBq. Renaud et al. reported a dynamic range of 230 MBq for the predecessor of the Ingenuity TF, the Gemini TF (Philips Healthcare),⁴ as shown in Table 1. As only the electronics were improved in the Ingenuity TF,⁸ it is reasonable to assume that the dynamic range only slightly improved in this newer PET system.

In addition to the Gemini TF, Renaud et al. also reported the dynamic ranges for the D690 and several other PET scanners,⁴ as shown in Table 1. They reported a dynamic range for the D690 of 570 MBq in their first experiment and 605 MBq in their second experiment. These experiments are in reasonable agreement with the 650 MBq that we measured, especially when considering the reproducibility error of 7% as reported by Renaud et al. and that we applied linear

interpolation between the measured activities. Consequently, our results are expected to be systematically higher (up to more than 10%) than those reported by Renaud et al. In addition, they also reported the dynamic range of a Biograph mCT (Siemens) system which was the PET system with the best count-rate performance in their study. This system had a dynamic range of 720 MBq, as shown in Table 1. As Renaud et al. used a comparable methodology, these results can be compared to our measurements. Hence, it seems that despite the better timing- and spatial resolutions of digital PET^{5,6}, the gain in dynamic range seems limited in comparison with the newest PET systems from other vendors. However, the count-rate performance of the digital PET prototype seems less affected at higher activities, and the applied dead-time correction is much lower in comparison with the conventional PET systems, as shown in Figure 1C. This may provide correction possibilities to further improve the dynamic range for digital PET. Yet one should also note that these activities may already lie outside the minimally required Rb-82 activities when using the state-of-the-art PET systems.

In relation to image quality assessed as the nonuniformity of the cardiac insert, we observed similar results as previously reported by Renaud et al.⁴ We also observed that the mean COV varies between different systems, possibly due to the use of different

reconstruction methods, but remains constant at least up to the dynamic range. This indicates that the image quality is not compromised up to the dynamic range. Our measurements show that the image quality of the D690 starts to degrade at activities > 1400 MBq, whereas Renaud et al. reported > 750 MBq. This difference is most likely due the different methodology as a result of using a different software.

Considerations

First, we primarily used the dynamic range to compare the count-rate performance of multiple PET systems. However, the threshold of 10% remains arbitrary, as its effect on the accuracy of MBF quantification is still unknown. Moreover, when not using linear interpolation to calculate the dynamic range, the dynamic range can be ± 70 MBq lower when the 10% cutoff just falls outside a 15 s time frame. As we applied linear interpolation in contrast to Renaud et al., this makes our results not fully comparable and may explain the differences of 49–84 MBq in dynamic range for the D690.⁹ Furthermore, one should not only be aware of the margin of error surrounding the dynamic range but also on its exact definition. In this study, we defined the dynamic range as the maximal *measured* activity. The corresponding maximal *true present* activity is therefore 10% higher, as shown in Table 1. The final consideration of our study is that the dynamic range or maximal measurable activity as determined in this study cannot directly be translated to patients.^{9,10} When calculating the maximal activity per equivalent body weight for the phantom and extrapolating this to a weight-based patient-specific protocol, this extrapolation can result in count rates or measured activities exceeding the dynamic range in patients.^{9,10} Hence, one needs to validate the final weight-based activity protocol by comparing it to patient scans for each individual scanner and to correct for possible differences before implementation.⁹

CLINICAL IMPLICATIONS

As mentioned above, the maximal activities as derived in the phantom study cannot directly be translated to patient studies.^{9,10} The dynamic ranges are often an underestimation of the maximal activity to be used in patients due to the lower attenuation and lack of activity distribution in the phantom. Renaud et al. previously reported this underestimation to be a factor 1.3 for a patient of 80 kg for the D690, resulting in a maximal activity to administer of 720 MBq (9 MBq·kg)⁹. For the Ingenuity TF, the count rate was 2811 kcps at the dynamic range. Combining this with our previously

published count-rate data in patients using the Ingenuity TF suggests that for an average patient of 80 kg, a fixed activity of ± 230 MBq should be used (see a tutorial on how to translate the phantom results to a patient protocol in Appendix 1).¹⁰ This implies that even with the minimal required activity of 740 MBq,¹¹ the Ingenuity TF seems unsuitable for MBF quantification when using the 10% bias as cutoff. Although patient data with the digital PET is lacking and we were unable to validate the derived activity for a patient protocol, this system is expected to perform in a comparable range as the D690. Yet additional corrections might improve the operating range of the digital PET in the near future.

NEW KNOWLEDGE GAINED

Myocardial blood flow quantification may be inaccurate at injected Rb-82 activities higher than approximately 350 MBq for the Ingenuity TF, and 700 MBq for the D690 and the digital PET prototype. Although myocardial blood flow quantification may be inaccurate at injected Rb-82 activities higher than approximately 700 MBq for the digital PET prototype, its limited activity bias and dead-time factor may provide correction possibilities to improve the dynamic range.

CONCLUSION

The maximal Rb-82 activity for MBF assessment using digital PET prototype (Philips Healthcare) is higher than that for its analog counterpart (Ingenuity TF), but seems comparable with the analog D690 PET system (GE Healthcare).

Disclosures

This work was supported by a research exhibit with Philips Healthcare. The content of the article was solely the responsibility of the authors. Maryam Khodaverdi is a clinical scientist of Philips Healthcare. All other authors have no additional conflicts of interest.

APPENDIX

HOW TO TRANSLATE THE PHANTOM RESULTS INTO A PATIENT PROTOCOL?

Several steps need to be undertaken to translate the dynamic range as determined in a phantom study into a patient protocol. Although a body-weight-dependent activity protocol is recommended, not all generators

are suitable for this. We therefore provide two approaches below. In both cases, we hypothesize that the difference between the true and measured activities up to 10% is acceptable for reliable MBF quantification.

STEP-WISE APPROACH

- (1) Derive the prompt count rate (counts per second, cps) of the PET system at the dynamic range using the anthropomorphic torso phantom.^{4,9,10}
- (2) Determine the maximal prompt count rates in a patient cohort: more than 50 patients are advised due to the relatively high variability.
- (3) Normalize these prompt count rates to (A) the administered activity (cps/MBq) for a fixed protocol or to (B) the activity and body weight (cps/MBq·kg) for a patient-specific activity protocol. Next, calculate the 95%-confidence interval (CI) upper limit of one of these normalized count rates in patients.
- (4) Divide the prompt count rate at the dynamic range of the phantom by the upper limit of the 95%-CI of the normalized maximal patient count rates to derive the maximal activity to be administered still resulting in reliable imaging.

Example: the prompt count rate at the dynamic range of the Ingenuity TF was 2811 kcps. The 95%-CI upper limit of the count rates normalized to activity (A) in a patient cohort previously studied¹⁰ was 11.7 kcps/MBq. This resulted in a maximal fixed activity protocol in patients of $2811/11.7 = 241$ MBq. In addition, the 95%-CI upper limits of the count rates normalized to activity and body weight (B) were 934 kcps/MBq·kg. This resulted in a maximal patient-specific activity protocol for the Ingenuity TF of $2811/934 = 3.0$ MBq·kg.^{9,10}

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