Time-frame sampling for ^{82}Rb PET flow quantification: Towards standardization of clinical protocols

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A growing body of literature is demonstrating the incremental prognostic and diagnostic value of myocardial blood flow (MBF) quantification over traditional myocardial perfusion imaging (MPI). With ^{82}Rb PET, MBF can be conveniently added to a standard MPI study with no additional cost or radiation dose, as the required technologies have reached a level of maturity and adoption enabling routine clinical application. Nevertheless, successful implementation of MBF quantification requires optimization of specific technical factors to achieve accurate and precise MBF measurements.¹ Example factors which have been previously investigated include pharmacologic stress hyperemia,² tracer administration profile,^{3,4} image reconstruction method,⁵ and tracer kinetic modeling.⁶ One factor which has received relatively little attention is time-frame binning of the raw data to produce dynamic image sequences from which MBF is quantified. The uninitiated may be forgiven for naively assuming that fine temporal sampling, with many short time-frames, is always advantageous over using few, long time-frames; upon further consideration of practical and physical

implications, selection of the optimal time-frame binning protocol may not be trivial. A review of the literature, as summarized in Table 1, clearly demonstrates a lack of standardization of dynamic imaging sequences in the literature.

From a practical standpoint, more sampled time-frames require more data storage and more computational power. On current clinical systems, long image reconstruction times can create a bottleneck to clinical throughput. Consider a PET system that adequately meets the needs of an oncology clinic performing whole-body FDG PET-CT with 45-minute time slots per patient. Each patient may be scanned at 10 bed positions, thus requiring reconstruction of 10 individual images. A complete cardiac perfusion study consists not only of the dynamic image sequence needed for MBF quantification, but also of static and cardiac-gated uptake images for traditional MPI interpretation, both at rest and stress states. Typically, this may include reconstructions of 15–30 dynamic time-frames, 8 cardiac phases, and 2 static images (before and after CTAC alignment), all repeated at rest and stress for a total of 50–80 images per patient. If the total reconstruction time exceeds 45 minutes, then a backlog develops which may preclude timely interpretation. Clearly, some compromises must be made for a cardiac protocol including routine MBF quantification to be clinically feasible on the same oncology system, even with state-of-the-art PET systems, where reconstruction hardware is typically underpowered for sustained patient throughput. One such compromise is to reduce the number of dynamic time-frames.

In this issue of the Journal, Lee et al. investigated the effect of varying dynamic PET time-frame lengths on MBF bias and precision, and proposed an optimal

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Table 1. Literature demonstrating a wide range of time-frame protocols in PET MBF quantification

Author	Tracer	Scan time (minutes)	Number of frames and frame lengths
Anagnostopoulos 2008 ⁷	^{82}Rb	6	26: 18 × 5, 6 × 15, 1 × 120, 1 × 60 seconds
Dahl 1996 ⁸	^{82}Rb	8	15: 12 × 10, 3 × 120 seconds
deKemp 2000 ⁹	^{82}Rb	10	24: 15 × 6, 5 × 12, 1 × 30, 1 × 60, 1 × 120, 1 × 240 seconds
deKemp 2013 ¹⁰	^{82}Rb	6	14: 9 × 10, 3 × 30, 1 × 60, 1 × 120 seconds
		6	16: 12 × 10, 2 × 30, 1 × 60, 1 × 120 seconds
		6	26: 12 × 5, 6 × 10, 4 × 20, 4 × 40 seconds
Efsaeff 2014 ⁵	^{82}Rb	6	14: 9 × 10, 3 × 30, 1 × 60, 1 × 120 seconds
		10	15: 9 × 10, 3 × 30, 1 × 60, 1 × 120, 1 × 240 seconds
El Fakhri 2009 ¹¹	^{82}Rb	7	27: 14 × 5, 6 × 10, 3 × 20, 3 × 30, 1 × 90 seconds
Goudarzi 2011 ¹²	^{82}Rb	8	32: 20 × 6, 5 × 12, 4 × 30, 3 × 60 seconds
Herrero 1992 ¹³	^{82}Rb	6.5	28: 18 × 5, 10 × 30 seconds
Knešarek 2009 ¹⁴	^{82}Rb	8	50: 36 × 5, 8 × 15, 6 × 30 seconds
Lortie 2007 ¹⁵	^{82}Rb	10	17: 12 × 10, 2 × 30, 1 × 60, 1 × 120, 1 × 240 seconds
Parkash 2004 ¹⁶	^{82}Rb	10	24: 15 × 6, 5 × 12, 1 × 30, 1 × 60, 1 × 120, 1 × 240 seconds
Renaud 2013 ¹⁷	^{82}Rb	10	24: 15 × 6, 5 × 12, 1 × 30, 1 × 60, 1 × 120, 1 × 240 seconds
Tahari 2014 ¹⁸	^{82}Rb	7	27: 20 × 6, 4 × 30, 3 × 60 seconds
Ziadi 2012 ¹⁹	^{82}Rb	10	17: 12 × 10, 2 × 30, 1 × 60, 1 × 120, 1 × 240 seconds

binning protocol that achieves high precision, low bias, and minimal computer resource requirements. Using computer simulations and clinical data, they propose an optimal time-frame binning protocol with minimal compromise of MBF accuracy and precision (24×5 seconds + 2×120 seconds = 26 time-frames over 6 minutes total). Furthermore, the authors proposed a relatively simple method, using Fourier analysis of the finely sampled arterial blood time-activity curve (TAC), which can be applied to estimate the required sampling interval, T_s , according to the shape of the blood TAC. They further propose an even simpler method, using the full-width at half-maximum (FWHM) of the blood peak to estimate T_s . A strong linear correlation between the two metrics was demonstrated ($R = 0.926$).

A few points of reflection to consider:

IS SAMPLING FREQUENCY THE WHOLE STORY?

Lee et al. attributed the bias and loss of precision in MBF measurements to inadequate temporal sampling according to the Nyquist theory, but it is conceivable that several other factors may have had influence. Random coincidence events and deadtime losses must be corrected for accurate image reconstruction and

quantification of tracer concentration. Depending on a specific vendor's implementation of these corrections, they may be applied as average values per time-frame, and not at fine time intervals (i.e., the PET scanner may not be accurately modeled as a simple integration over a time-frame interval). During time intervals consisting of rapidly changing activity (i.e., near the peak blood activity), these inaccuracies will be most pronounced, especially for a tracer such as ^{82}Rb where T_s can be a substantial fraction of the 76-second half-life.

WHAT ABOUT ACCURACY?

A limitation of Lee's work is that no reference truth standard existed for evaluating the accuracy of MBF values. Instead, the highest sampling rate data (2-second time-frames) were assumed to be true. However, short time-frames consist of fewer coincidence events and therefore contain more noise, which can also lead to bias in reconstructed activity and/or MBF measurements. Nevertheless, the consistent response of the average error curves below 15 second time-frames is encouraging in this dataset, but may not be representative of other imaging systems. The use of a flow phantom²⁰ may be beneficial for validating MBF accuracy.

Figure 1. Left ^{82}Rb infusion profiles for the CA-CF test-retest cohort. The CA-mode elution profiles follow an approximate ‘square-wave’ infusion profile with a constant activity-rate of 0.33 MBq/s/kg, resulting in a consistent total injected activity of 10 MBq/kg (shaded blue area) administered over a standard time interval of 30 seconds. The CF-mode profiles result in the same total activity, but injected over variable time intervals from 10 to 30 seconds and with variable peak amplitudes from 0.4 to 2.2 MBq/s/kg. Right Resulting blood time-activity curves. Left is reproduced from Ref. 3.

Table 2. FWHM (seconds) and regression-derived sampling rate T_s (seconds) of blood time-activity curve bolus using constant flow-rate and constant activity-rate elutions compared to the results of Lee et al.

	FWHM (seconds)		T_s (95%) (seconds)	
	Rest	Stress	Rest	Stress
Lee (2-second time-frames)				
50 mL/min bolus	13 ± 5	12 ± 6	12.5	11.7
Klein (10-second time-frames)				
30 mL/min constant flow-rate	21 ± 5	19 ± 6	18.8	16.9
0.33 MBq/s/kg constant activity-rate	39 ± 12*	38 ± 4*	31.9	31.6

* $P < 0.05$ paired t test vs constant flow-rate.

ALTERNATIVE TRACER ADMINISTRATION?

The results of Lee et al. are most relevant to the current commercial rubidium generator system, using “constant flow-rate” (CF) injections that elute the generator at a fixed, high rate of saline flow to produce a relatively sharp bolus of activity, but which vary in duration and shape depending on age of the generator and requested activity. They discuss briefly the use of the so-called “constant activity-rate” (CA) slow-bolus administration of ^{82}Rb activity, which may reduce the sampling requirements further. We have previously reported an automated infusion system that delivers ^{82}Rb at a constant rate of activity [MBq/s] over a standard 30-second interval, regardless of generator age.²¹ These consistent infusion profiles lead to more reproducible

MBF measurements and improved test-retest repeatability (standard error $\approx 10\%$).^{3,6} Slow-bolus or CA tracer infusions may enable the ability to administer larger ^{82}Rb activities on count-rate-limited PET systems (e.g., fully 3D systems or BGO crystals) while avoiding saturation in the early blood-pool phase of a dynamic study.^{4,22} The scanner encounters lower peak count rates (prompt and random coincidences) and more gradual fluctuations. Thus, depending on camera vendor-specific implementation, time-averaged deadtime, and random coincidences, corrections may be more accurate for longer time-frames.

To compare between CA and CF infusion modes, we applied Lee’s methods to the test-retest MBF repeatability data previously published by our group.³

The data consisted of dynamic image sequences (9×10 , 3×30 , 1×60 , 1×120 seconds time-frames) from a single imaging session consisting of rest-CA, rest-CF, stress-CA, and stress-CF back-to-back ^{82}Rb PET-CT imaging in a small cohort of 9 patients (36 scans in total). Figure 1 shows the time-activity elution profiles reported by the infusion system and the resulting blood time-activity curves. The results in Table 2 confirm broader blood peaks (larger FWHM) with CA elutions vs CF elutions. The sampling rate preserving 95% of the signal power, $T_s(95\%)$, was estimated using the relationship described by Lee et al ($T_s(95\%) = 0.753 \times \text{FWHM} + 2.391$). FWHM measures were larger in our data, even with the shorter CF infusions compared to those of Lee, likely due to longer time-frames (10 vs 2 seconds), as also demonstrated in Figure 1 of the Lee paper. These results support our hypothesis that fewer, longer time-frames (e.g., 30 seconds) might be used with the slow-bolus CA infusions without loss of precision and accuracy, if Nyquist sampling is the only factor at play.

A potential down-side of longer infusion profiles is that the blood peak is extended later into the dynamic image sequence, requiring more short time-frames to accurately sample the shape of the blood peak clearance. This was evident in one of our rest-CA studies with a 72 seconds FWHM (a clear outlier in the data) which was partially attributed to 30-second intermediate time-frame sampling at the end of the blood peak.

Regardless of the infusion profile, Lee's method effectively rules out the need for <5-second time-frames using current technology, and their proposed 2-phase protocol forms a robust starting point for any laboratory looking to implement a ^{82}Rb PET MBF clinical protocol. Further simplification, using longer frames, may also be feasible with slow-bolus constant activity-rate infusions.

Disclosure

R. Klein and R. deKemp received royalties from the sales of FlowQuant software, flow quantification software licensed to Invia Medical Imaging Solutions, and rubidium generator technologies licensed to Jubilant DraxImage. They are consultants to Jubilant DraxImage. Adrian Ocneanu does not have any conflicts of interest to disclose.

References

- Moody JB, Lee BC, Corbett JR, Ficaro EP, Murthy VL. Precision and accuracy of clinical quantification of myocardial blood flow by dynamic PET: A technical perspective. *J Nucl Cardiol.* 2015;22:935–51.
- Johnson NP, Gould KL. Regadenoson versus dipyridamole hyperemia for cardiac PET imaging. *JACC Cardiovasc Imaging.* 2015;8:438–47.
- Klein R, Ocneanu A, Renaud JM, Ziadi MC, Beanlands RSB, deKemp RA. Consistent tracer administration profile improves test–retest repeatability of myocardial blood flow quantification with ^{82}Rb dynamic PET imaging. *J Nucl Cardiol.* 2016. doi:10.1007/s12350-016-0698-6.
- Renaud JM, Yip K, Guimond J, Trottier M, et al. Characterization of 3D PET systems for accurate quantification of myocardial blood flow. *J Nucl Med.* 2016;58:103–9. doi:10.2967/jnumed.116.174565.
- Efseaff M, Klein R, Ziadi MC, Beanlands RS, deKemp RA. Short-term repeatability of resting myocardial blood flow measurements using rubidium-82 PET imaging. *J Nucl Cardiol.* 2012;19(5):997–1006. doi:10.1007/s12350-012-9600-3.
- Ocneanu AF, deKemp RA, Renaud JM, Adler A, Beanlands RSB, Klein R. Optimally repeatable kinetic model variant for myocardial blood flow measurements with ^{82}Rb PET. *Comput Math Methods Med.* 2017;2017:1–11.
- Anagnostopoulos C, et al. Quantitative relationship between coronary vasodilator reserve assessed by ^{82}Rb PET imaging and coronary artery stenosis severity. *Eur J Nucl Med Mol Imaging.* 2008;35(9):1593–601.
- vom Dahl J, Muzik O, Wolfe ER, Allman C, Hutchins G, Schwaiger M. Myocardial rubidium-82 tissue kinetics assessed by dynamic positron emission tomography as a marker of myocardial cell membrane integrity and viability. *Circulation.* 1996;93:238–45.
- deKemp RA, Ruddy TD, Hewitt T, Dalipaj MM, Beanlands RS. Detection of serial changes in absolute myocardial perfusion with ^{82}Rb PET. *J Nucl Med.* 2000;41:1426–35.
- deKemp RA, et al. Multisoftware reproducibility study of stress and rest myocardial blood flow assessed with 3D dynamic PET/CT and a 1-tissue-compartment model of ^{82}Rb kinetics. *J Nucl Med.* 2013;54:571–7.
- El Fakhri G, et al. Reproducibility and accuracy of quantitative myocardial blood flow assessment with ^{82}Rb PET: Comparison with ^{13}N -ammonia PET. *J Nucl Med.* 2009;50(7):1062–71.
- Goudarzi B, Fukushima K, Bravo P, Merrill J, Bengel FM. Comparison of the myocardial blood flow response to regadenoson and dipyridamole: A quantitative analysis in patients referred for clinical ^{82}Rb myocardial perfusion PET. *Eur J Nucl Med Mol Imaging.* 2011;38(10):1908–16.
- Herrero P, Markham J, Shelton ME, Bergmann SR. Implementation and evaluation of a two-compartment model for quantification of myocardial perfusion with rubidium-82 and positron emission tomography. *Circ Res.* 1992;70(3):496–507.
- Knešarek K, Machac J, Zhang Z. Repeatability of regional myocardial blood flow calculation in ^{82}Rb PET imaging. *BMC Med Phys.* 2009;9(1):2.
- Lortie M, Beanlands RSB, Yoshinaga K, Klein R, DaSilva JN, deKemp RA. Quantification of myocardial blood flow with ^{82}Rb dynamic PET imaging. *Eur J Nucl Med Mol Imaging.* 2007;34:1765–74.
- Parkash R, et al. Potential utility of rubidium 82 pet quantification in patients with 3-vessel coronary artery disease. *J Nucl Cardiol.* 2004;11(4):440–9.
- Renaud JM, DaSilva JN, Beanlands RSB, DeKemp RA. Characterizing the normal range of myocardial blood flow with ^{82}Rb and ^{13}N -ammonia PET imaging. *J Nucl Cardiol.* 2013;20(4):578–91.

18. Tahari AK, et al. Absolute myocardial flow quantification with ^{82}Rb PET/CT: Comparison of different software packages and methods. *Eur J Nucl Med Mol Imaging*. 2014;41(1):126–35.
19. Ziadi MC, et al. Does quantification of myocardial flow reserve using rubidium-82 positron emission tomography facilitate detection of multivessel coronary artery disease? *J Nucl Cardiol*. 2012;19(4):670–80.
20. Gabrani-Juma H, Clarkin O, Pourmoghaddas A, deKemp R, Wells RG, Klein R. A novel multi-modality perfusion phantom for nuclear imaging studies. *J Nucl Med*. 2015;56(supplement 3):437–437.
21. Klein R. Precise ^{82}Rb infusion system for cardiac perfusion measurement using 3D positron emission tomography. Ottawa, ON: University of Ottawa; 2005.
22. Klein R, Beanlands RSB, deKemp RA. Quantification of myocardial blood flow and flow reserve: Technical aspects. *J Nucl Cardiol*. 2010;17:555–70.