⁸²Rb-PET MPQ: Do normal values exist?

Sergey V. Nesterov, MD, PhD, PMP, PgMP,^{a,b} and Juhani M. Knuuti, MD, PhD^a

^a Turku PET Centre, University of Turku, Turku, Finland

^b Institute of Evolutionary Physiology and Biochemistry RAS, St. Petersburg, Russia

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Introducing their recent study, Freitag et al.¹ state that “two questions remain unanswered for quantitative ⁸²Rb-PET: (1) which are the normal values of sMBF and rMBF? And (2) which quantitative parameter is the most accurate to allow for a precise diagnosis of CAD (sMBF or myocardial flow reserve [MFR])?”

To get an answer, they performed a study of 357 patients that underwent ⁸²Rb-PET/CT and integrated coronary CT angiography (CCTA). Based on the finding in CCTA, the patients were classified as (a) normal (no stenosis, N = 153), (b) with non-obstructive coronary artery disease (CAD) (< 50%, N = 99), and (c) with obstructive CAD (≥ 50%, N = 105). Not surprisingly, the global stress myocardial blood flow (sMBF) (and myocardial flow reserve, MFR) were higher 3.61 ± 0.71 mL·min⁻¹·g (3.08 ± 0.84) in normal patients than in patients with obstructive CAD 3.04 ± 0.77 mL·min⁻¹·g (2.68 ± 0.79). Yet they turned out to be not different compared to patients with non-obstructive CAD (3.43 ± 0.69 mL·min⁻¹·g and 2.99 ± 0.82). Also, sMBF was more accurate than MFR in identifying both ischemia and severe ischemia. The authors conclude that the provided “normal quantitative values”—3.5 mL·g⁻¹·min⁻¹—which they called the “optimal threshold,” can help rule out myocardial ischemia. Also, they suggest that a resting scan could be omitted in patients with sMBF values.

We will not hover over the question of favoring sMBF over MFR: the same has been shown for 15O-

water,^{2,3} and taking into account the reduced radioactive burden, it does seem an advantageous option. However, we would like to draw attention to the question of “normal values.” Naturally, practicing physicians do crave the certainty that a number—a cutoff value here—promises to provide.

The authors used CT coronary angiography to rule out CAD in patients with suspected ischemic heart disease. Therefore, the selection of the patients can be assumed to represent the population that is typically entering diagnostic testing for suspected obstructive CAD with the caveat that potential microvascular disease remains undetected. The findings of the current study are not very different from the previous small study by Prior et al.,⁴ where the normal sMBF was 3.82 ± 1.21 mL·min⁻¹·g (9% higher than the Freitag's), in a younger population (age— 30 ± 13 years). On the other hand, a more extensive study (N = 241) by Johnson and Gould⁵ on even the younger population (age— 28 ± 5 years) provided the normal sMBF of 2.71 ± 0.58 mL·min⁻¹·g—value smaller by almost a quarter (– 23%) than in the current study. Yet another small study⁶ reported “normal” sMBF values as low as 1.72 ± 0.41 mL·min⁻¹·g.

Several factors can explain the variability in published normal values in quantitative ⁸²Rb-PET. The patient populations may differ as many of the earlier studies have been performed in young people. Also, we again^{7,8} attract the attention of the readership to the fundamental fact that all absolute values in PET perfusion imaging—normal and not—result from the transformation process. The measured radioactivity concentration values turn into milliliters of blood per minute per gram of myocardial tissue (mL·min⁻¹·g). The process is done with dedicated software tools. It consists of several steps, and each of the steps can and does affect the results (for the detailed analysis, see⁷). This process is less standardized that we would all want it to be: even such primary thing as the exact definition of the LV base is not clear in the 17-AHA segmentation.⁹ Each software tool will solve the problem in its way, and it can affect the results.

Reprint requests: Sergey V. Nesterov, MD, PhD, PMP, PgMP, Turku PET Centre, University of Turku, Turku, Finland; sergey.nesterov@tyks.fi

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In our cross-comparison study of ten software packages analyzing exactly Rb-82,¹⁰ we found that the differences in the results obtained with different tools can be well over 100%. The three earlier papers that had ended up with such different results to get their “normal values” used three various software tools. The current study (1) utilized the forth one—Syngo MBF. Indeed, those tools that implemented the same tracer kinetic approach, as in,¹¹ (the “OHI-1-TCM” in¹⁰) in our study showed similar results. And it is indeed reassuring to see that the closest “normal values” to the Freitag’s 3.61 ± 0.71 mL·min⁻¹·g—Prior’s 3.82 ± 1.21 mL·min⁻¹·g come from different software (PMOD), yet the one implementing the same tracer kinetic approach.

One of the main limitations of the current paper is that the authors try to derive a cutoff value for the quantitative sMBF and MFR from the data, calling it an “optimal threshold” to rule out myocardial ischemia. The problem arises from the fact that there was no reference standard for ischemia. It is well known that CCTA is excellent in ruling out obstructive CAD but is not accurate in ruling out ischemia. Therefore, the patients with the disease do not represent the actual population with ischemia. The threshold estimation is consequently subject to significant bias. Accordingly, the authors reported that using the threshold of 3.5 mL·g·min, the negative predictive value for obstructive CAD was 96%, but the positive predictive value was as low as 22%. These results mean that 78% of patients who got sMBF below 3.5 mL·g·min did not have an obstructive CAD. The correct way to estimate ideal cutoff is to have an appropriate functional reference standard, as done by Danad et al.,¹² using O15-water PET.

The second main limitation is that the focus was primarily on global values. The focus is understandable as the authors did not have an appropriate reference standard for regional ischemia. CAD is a regional disease, though, and global sMBF and MFR values are insensitive for regionally limited ischemia. The cutoff values for regional ⁸²Rb-PET results would require a reference standard with regional results. It can be expected that the optimal regional cutoffs for ischemia are clearly lower than the values reported in the current paper.

Concluding, we think that the current study provided useful information about the question, “*which are the normal values of sMBF and rMBF?*” albeit with some limitations as explained above. The finding that sMBF is more accurate than MFR also with ⁸²Rb-PET also sounds rational and agrees with earlier findings. However, the current study cannot answer the question of what are the optimal cutoffs to separate patients with ischemia from those without. Further studies with an appropriate reference standard and also regional analysis are warranted.

References

- Freitag MT, Bremerich J, Wild D, Haaf P, Zellweger MJ, Caobelli F (2020) Quantitative myocardial perfusion ⁸²Rb-PET assessed by hybrid PET/coronary-CT: Normal values and diagnostic performance. *J Nucl Cardiol*. <https://doi.org/10.1007/s12350-020-02264-4>
- Joutsiniemi E, Saraste A, Pietilä M, Mäki M, Kajander S, Ukkonen H et al (2014) Absolute flow or myocardial flow reserve for the detection of significant coronary artery disease? *Eur Heart J Cardiovasc Imaging* 15:659-665. <https://doi.org/10.1093/ehjci/je1274>
- Danad I, Raijmakers PG, Appelman YE, de Harms HJ et al (2013) Hybrid imaging using quantitative H215O PET and CT-based coronary angiography for the detection of coronary artery disease. *J Nucl Med* 54:55-63. <https://doi.org/10.2967/jnumed.112.104687>
- Prior JO, Allenbach G, Valenta I, Kosinski M, Burger C, Verdun FR et al (2012) Quantification of myocardial blood flow with ⁸²Rb positron emission tomography: Clinical validation with ¹⁵O-water. *Eur J Nucl Med Mol Imaging* 39:1037-1047. <https://doi.org/10.1007/s00259-012-2082-3>
- Johnson NP, Gould KL (2012) Integrating noninvasive absolute flow, coronary flow reserve, and ischemic thresholds into a comprehensive map of physiological severity. *JACC Cardiovasc Imaging* 5:430-440. <https://doi.org/10.1016/j.jcmg.2011.12.014>
- El Fakhri G, Kardan A, Sitek A, Dorbala S, Abi-Hatem N, Lahoud Y et al (2009) Reproducibility and accuracy of quantitative myocardial blood flow assessment with (⁸²Rb) PET: Comparison with (¹³N)-ammonia PET. *J Nucl Med* 50:1062-1071. <https://doi.org/10.2967/jnumed.104.007831>
- Nesterov SV, Lee BC, Moody JB, Slomka P, Han C, Knuuti JM (2016) The status and future of PET myocardial blood flow quantification software. *Ann Nucl Cardiol* 2:106-110. <https://doi.org/10.17996/ANC.02.01.106>
- Nesterov SV, Knuuti J (2018) How accurate is the accuracy? *J Nucl Cardiol*. <https://doi.org/10.1007/s12350-018-01537-3>
- Cerqueira MD, Weissman N, Dilsizian V, Jacobs AK, Kaul S, Laskey WK et al (2002) Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 105:539-542. <https://doi.org/10.1161/hc0402.102975>
- Nesterov SV, Deshayes E, Sciagrà R, Settimo L, Declerck JM, Pan XB et al (2014) Quantification of myocardial blood flow in absolute terms using (⁸²Rb) PET imaging: The RUBY-10 study. *JACC Cardiovasc Imaging* 7:1119-1127. <https://doi.org/10.1016/j.jcmg.2014.08.003>
- Lortie M, Beanlands RS, Yoshinaga K, Klein R, DaSilva JN, DeKemp RA (2007) Quantification of myocardial blood flow with ⁸²Rb dynamic PET imaging. *Eur J Nucl Med Mol Imaging* 34:1765-1774. <https://doi.org/10.1007/s00259-007-0478-2>
- Danad I, Uusitalo V, Kero T, Saraste A, Raijmakers PG, Lammertsma AA et al (2014) Quantitative assessment of myocardial perfusion in the detection of significant coronary artery disease: Cut-off values and diagnostic accuracy of quantitative (¹⁵)OH₂O PET imaging. *J Am Coll Cardiol* 64:1464-1475. <https://doi.org/10.1016/j.jacc.2014.05.069>

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