Quantitative myocardial blood flow imaging: not all flow is equal

Paul Knaapen

Received: 23 September 2013 / Accepted: 23 September 2013 / Published online: 22 October 2013
© Springer-Verlag Berlin Heidelberg 2013

Myocardial perfusion imaging (MPI) is routinely utilized to noninvasively evaluate patients with suspected or known coronary artery disease (CAD). Although a large armamentarium of imaging techniques is available for this purpose, PET has been shown to possess the highest diagnostic accuracy in detecting CAD [1]. Traditionally, these MPI images are graded in a qualitative manner whereby perfusion defects are identified based on the relative distribution of the tracer. Unfortunately, in conditions with a lack of normal myocardium to act as a reference, such a qualitative approach may yield false-negative results or underestimate the extent of disease (e.g. in multivessel disease and/or microvascular dysfunction). PET, however, additionally offers the possibility to quantify myocardial blood flow (MBF) in absolute terms (i.e. millilitres per minute per gram) when images are acquired in a dynamic fashion [2]. Until recently, quantification of myocardial perfusion was primarily regarded as a research tool because it involved elaborate and time-consuming postprocessing procedures. Advances in PET systems have overcome these limitations and commercially available software packages currently generate quantitative MBF images in the order of minutes with high reproducibility [3]. As a consequence, absolute quantification of flow has ushered into the clinical arena. When interpreting these values,

one is immediately faced with the question: what constitutes normal (hyperaemic) MBF? Unfortunately, this issue is not straightforward.

Recently, Gould et al. comprehensively summarized the available literature on quantitative myocardial perfusion PET in a review including thousands of normal controls as well as patients with CAD [4]. These data have taught us that baseline MBF remains relatively constant ($0.82 - 0.85 \text{ mL min}^{-1} \text{ g}^{-1}$), whereas hyperaemic MBF gradually decreases from healthy controls (about $2.89 \pm 1.29 \text{ mL min}^{-1} \text{ g}^{-1}$), to individuals with traditional CAD risk factors (about $2.25 \pm 1.07 \text{ mL min}^{-1} \text{ g}^{-1}$), to patients with overt CAD (about $1.71 \pm 0.71 \text{ mL min}^{-1} \text{ g}^{-1}$). These observations in various stages of CAD are of interest, but do not provide an answer as to when hyperaemic MBF can be deemed abnormal in an individual patient screened for CAD. The detection of haemodynamically significant CAD is based on the presence of a flow-limiting epicardial coronary lesion, whereas PET MBF measurements reflect the composite of perfusion throughout the entire coronary artery tree (roughly divided into the epicardial coronary compartment and the microvasculature, see Fig. 1). Therefore, knowledge of the variability and determinants of the microvascular component of total coronary resistance is of importance to further define the normal limits of quantitative MBF imaging.

In the December 2013 issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, Liga et al. explore the determinants of hyperaemic MBF using dipyridamole $^{13}\text{NH}_3$ PET in symptomatic patients suspected of having CAD, but in whom significant epicardial lesions have been excluded by invasive or CT-based coronary angiography [5]. Such a cohort thus

P. Knaapen (✉)
Department of Cardiology, VU University Medical Center,
De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands
e-mail: p.knaapen@vumc.nl

Fig. 1 Representation of the coronary vascular bed, divided into the epicardial conduit arteries and the microvasculature. Resistance is principally determined by the microvasculature and vasomotor function is influenced by gender, age, and cardiovascular risk profile. The detection of CAD is based on the functional evaluation of an epicardial stenosis. Quantitative MPI provides an integrated measurement of perfusion in the entire coronary vascular bed, whereas fractional flow reserve (FFR), for example, measures solely the pressure gradient across the coronary lesion. FFR and perfusion imaging therefore provide different information on coronary vascular health and are not necessarily concordant [10]

represents a patient population encountered in daily practice and provides clinically relevant information, as opposed to databases of healthy controls. Out of 167 enrolled patients, 100 displayed normal coronary arteries, 41 nonsignificant atherosclerosis, and 26 significant CAD. As anticipated, a gradual decline in hyperaemic MBF was observed across the groups. Multivariate analysis revealed that insulin resistance, the presence of atherosclerosis, and male sex were independently related to impaired hyperaemic perfusion. Upon exclusion of patients with atherosclerosis, gender-related differences in coronary microvascular function remained substantial. Last year, a comparable study by Danad et al. was published in this journal [6]. Although both studies linked a number of traditional cardiovascular risk factors to coronary microvascular dysfunction, the most prominent similarity between them is the impact of gender. These results suggest that in analogy to other clinical parameters

Fig. 2 Kinetics of myocardial perfusion tracers showing the relationship between absolute MBF of PET radiotracers and actual tracer uptake. ^{18}F -Flurpiridaz is not yet available for clinical use

(e.g. coronary calcium scoring), interpretation of perfusion values may require correction for gender.

Comparison of these studies also highlights important methodological issues of quantitative perfusion PET. Liga et al. found hyperaemic MBF values using dipyridamole $^{13}NH_3$ PET in men and women of 1.17 ± 0.47 and 1.42 ± 0.45 mL min⁻¹ g⁻¹, respectively, while Danad et al. reported notably higher values with adenosine $H_2^{15}O$ PET of 2.90 ± 0.85 and 3.78 ± 1.27 mL min⁻¹ g⁻¹, respectively. These major discrepancies in seemingly comparable cohorts of patients were most likely due to the vasodilator and flow tracer utilized. Adenosine appears to induce more potent vasodilation than dipyridamole and these agents should not be considered interchangeable [7]. Perhaps even more profound is the impact of flow tracer utilized. Currently, three PET perfusion tracers are available ($H_2^{15}O$, $^{13}NH_3$, and ^{82}Rb). As shown in Fig. 2, $H_2^{15}O$ is the only freely diffusible tracer that can be completely extracted from arterial blood, rendering it ideal for quantifying perfusion, as all observed changes in myocardial tracer activity are solely dependent on perfusion and not affected by flow-dependent rates of extraction [8]. In contrast, $^{13}NH_3$ and particularly ^{82}Rb display a roll-off phenomenon with a curvilinear extraction rate, resulting in progressive underestimation of MBF at increasing flow quantities.

Correction models for incomplete extraction of tracer can be employed, but induce noise. Even utilizing these models, however, reported perfusion values for specific patient populations gradually decline in parallel with tracer tissue extraction kinetics. In fact, results from studies that have attempted to define optimal cut-off values for hyperaemic MBF to identify significant CAD lack uniformity and clearly display a tracer-specific pattern, with values observed as low as 0.91 mL min⁻¹ g⁻¹ for ^{82}Rb and as high as 2.50 mL min⁻¹ g⁻¹ for $H_2^{15}O$ with an intermediate threshold range of $1.15 - 1.85$ mL min⁻¹ g⁻¹ for $^{13}NH_3$ [4]. As a consequence, tracer characteristics need to be taken into account when interpreting quantitative MBF obtained with PET.

The study by Liga et al. provides an important insight into the complexities of quantitative MBF imaging and clues as to what issues need to be addressed before its implementation in routine clinical use can be advocated. Future studies should focus on standardizing imaging protocols (regarding radionuclides, scanner hardware, stress agents, compartment models, etc.) and be conducted in a multicentre fashion in carefully selected cohorts of patients with appropriate reference standards to more clearly define the pathophysiological meaning of quantitative MBF on macro- and microvascular health, and help guide therapeutic decision-making to improve outcomes [4, 9].

References

1. Jaarsma C, Leiner T, Bekkers SC, Crijns HJ, Wildberger JE, Nagel E, et al. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. *J Am Coll Cardiol*. 2012;59:1719–28.
2. Knaapen P, Camici PG, Marques KM, Nijveldt R, Bax JJ, Westerhof N, et al. Coronary microvascular resistance: methods for its quantification in humans. *Basic Res Cardiol*. 2009;104:485–98.
3. Harms HJ, Knaapen P, de Haan S, Halbmeijer R, Lammertsma AA, Lubberink M. Automatic generation of absolute myocardial blood flow images using [¹⁵O]H₂O and a clinical PET/CT scanner. *Eur J Nucl Med Mol Imaging*. 2011;38:930–9.
4. Gould KL, Johnson NP, Bateman TM, Beanlands RS, Bengel FM, Bober R, et al. Anatomic versus physiologic assessment of coronary artery disease: guiding management decisions using positron-emission tomography (PET) as a physiologic tool. *J Am Coll Cardiol*. 2013. doi:10.1016/j.jacc.2013.07.076
5. Liga R, Rovai D, Sampietro T, Vecoli C, Todiere G, Caselli C, et al. Insulin resistance is a major determinant of myocardial blood flow impairment in anginal patients. *Eur J Nucl Med Mol Imaging*. 2013;40:1905–1913. doi:10.1007/s00259-013-2523-7.
6. Danad I, Raijmakers PG, Appelman YE, Harms HJ, de Haan S, van den Oever MLP, et al. Coronary risk factors and myocardial blood flow in patients evaluated for coronary artery disease: a quantitative [¹⁵O]H₂O PET/CT study. *Eur J Nucl Med Mol Imaging*. 2012;39:102–12.
7. Chareonthaitawee P, Kaufmann PA, Rimoldi O, Camici PG. Heterogeneity of resting and hyperemic myocardial blood flow in healthy humans. *Cardiovasc Res*. 2001;50:151–61.
8. Danad I, Raijmakers PG, Knaapen P. Diagnosing coronary artery disease with hybrid PET/CT: it takes two to tango. *J Nucl Cardiol*. 2013;20:874–90.
9. Gaemperli O, Lüscher TF, Bax JJ. View point: what should the future design of clinical imaging studies be? *Eur Heart J*. 2013;34:2432–5.
10. Johnson NP, Kirkeeide RL, Gould KL. Is discordance of coronary flow reserve and fractional flow reserve due to methodology or clinically relevant coronary pathophysiology? *JACC Cardiovasc Imaging*. 2012;5:193–202.