EDITORIAL

Myocardial perfusion models: A means or an end?

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Why do we model myocardial perfusion? The article by Alessio et al[1] in this issue offers a timely opportunity to consider two major, competing reasons. In turn, clarifying the motivations for modeling suggests clear next steps for cardiac positron emission tomography (PET) research.

Fundamentally, the myocardium cares about flow, not pressure.[2] Therefore, pressure-based fractional flow reserve (FFR) cannot provide a direct measurement of the absolute levels of perfusion and coronary flow reserve (CFR) that produce ischemia.[3,4] Indeed, the relationship between FFR and CFR, no matter how each is measured, reflects a complex interplay among focal disease, diffuse atherosclerosis, and small vessel dysfunction.[5] Yet FFR, while not perfect, has strong trial data behind it and remains clearly superior to anatomic-guided revascularization.[6] However, in addition to serving only as a surrogate for flow, FFR requires an invasive procedure. In contrast, quantification of absolute myocardial perfusion and flow reserve by cardiac PET offers a non-invasive alternative and measures flow directly. In short, modeling myocardial perfusion may ''build a better mousetrap'' for clinicians.

On the other hand, models of perfusion can clarify fundamental physiology. Every model contains assumptions regarding the structure and function of the coronary-myocardial system and also the interaction of the tracer with this system. Each assumption serves as an opportunity to further our understanding. For a system example, studies of microsphere distribution led prior investigators from the same University of Washington group as the current study to propose a fractal branching structure.[7] For a tracer example, time-activity curves can study metabolic changes of ammonia after injection.[8] Perfusion models, therefore, provide an experimental test of existing physiologic theories. In short, modeling myocardial perfusion allows physiologists to ''kick the tires'' and ''look under the hood.''

How well can myocardial perfusion models serve each purpose? Here, both intentions have common ground, namely distinguishing a signal (clinical or physiologic) from background noise. While much effort has been spent on choosing the ''best'' model to extract the signal of interest, we feel several broad factors have historically been neglected relative to their importance (see Table 1).

First, radionuclide decay has inherent Poisson statistical noise and physical resolution, the former exacerbated by short imaging blocks if using a time-activity curve method and the latter due to the positron range of tracers. Second, cardiac PET hardware and software introduces distortions due to the point-spread function, reconstruction algorithm, post-processing smoothing filters, and potential nonlinear response of the imaging system. Third, cardiac, respiratory, and abdominal content motion during supine acquisition smears out activity, unlike the perfectly stationary situation in brain PET imaging. Fourth, attenuation correction—regardless if acquired by rotating rod or computed tomography—can suffer from misregistration and in some cases offer an imperfect tradeoff between opposing myocardial segments[9] or compromise adjacent structures. Fifth, the arterial input necessary for any flow model also suffers from the preceding factors and imaging differences among potential anatomic locations (prior studies have used any combination of thoracic aorta, left atrium, or left ventricular blood pool).[10]

The exact radiotracer and flow model then seek a signal against a background of these five broad categories of noise. Each tracer has its own ''physiology'' as well. For example, oxygen-15 diffuses freely including into the blood pool, thereby necessitating some type of imaging processing removal, while nitrogen-13 ammonia undergoes a series of complex and time-dependent metabolic changes[8] that must be taken into consideration.

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Table 1. Broad categories of noise affecting all myocardial perfusion models

Category	Components
Statistical noise and physical resolution	Poisson counting from radioactive decay Positron range
PET imaging system	Point-spread function Reconstruction algorithm Post-processing smoothing filters Non-linear response and saturation
Motion	Cardiac cycle Respiratory cycle Settling of abdominal contents when supine
Attenuation correction	Misregistration Compromise of adjacent structures
Arterial input	Temporal noise Various anatomic locations

Flow models incorporate a range of physiologic sophistication. For example, three compartments (capillary, interstitial, and intracellular spaces) for nitrogen-13 ammonia are often simplified by combining interstitial and intracellular compartments.[11]

With the above context as a foundation, the new work by Alessio et al[1] can be better understood. Their motivation was primarily physiologic—to replace the more simple assumption of a uniformly homogenous tracer in the two- and three-compartment models with the more realistic assumption that tracer concentration varies along the axial length of each of two compartments (plasma and myocyte). These so-called distributed models may offer more realism, albeit at the price of increased model and computational complexity.

The main finding of interest is that both types of models performed similarly. Their work adds to prior literature that the exact flow model has only marginal importance for clinical decisions.[12] This result should be comforting for the clinician confronted with an array of potential software packages for estimating absolute flow and CFR by PET. Despite seemingly more realistic physiologic assumptions, the work of Alessio et al[1] could not show convincingly superior performance of a distributed model. Specifically, Bland-Altman analysis showed similar results for absolute flow (bias 0.03 cc/minute/g for distributed vs −0.03 cc/minute/g for three compartments, limits of agreement 1.35 cc/minute/g for distributed vs 1.05 cc/minute/g for three compartments) and CFR (bias 0.23 for distributed vs −0.16 for three compartments, limits of agreement 1.85 for distributed vs 1.64 for three compartments). Also, absolute blood flow error was similar between assumptions (0.03 ± 0.04 cc/minute/g for distributed vs −0.03 ± 0.03 cc/minute/g for three compartments) while CFR error was significantly worse (0.23 ± 0.08 for distributed vs 0.14 ± 0.07 for three compartments). While linear slopes were significantly better for absolute blood flow (0.98 for distributed vs 0.69 for three compartments) and CFR (0.92 for distributed vs 0.58 for three compartments), correlation coefficients were similar.

However, as their motivation was physiologic, we should ask why their experimental data could not distinguish between assumptions of homogenous tracer concentration and axially distributed tracer concentration. While on the face of it such a result may seem unexpected, it can easily be understood by recalling the five major categories of noise discussed above that limit the raw data used by any PET model of myocardial perfusion. Indeed the authors even write that the ''shapes of the model responses to sharp pulse inputs in the two cases are strikingly different, and give different estimates for tracer permeation kinetics, but relatively similar estimates of regional flows. With temporally-dispersed inputs and noisy data the distinctiveness of the shapes diminishes.''[1] Therefore, the competing physiologic assumptions are too fine to be distinguished based on PET data, even in the idealized setting of a dog model with highly controlled anesthesia, hemodynamics, and conditions of a completely patent versus total coronary occlusion.

As such, the article by Alessio et al[1] makes clear the next general steps for cardiac PET models of myocardial perfusion. First, their work indirectly emphasizes the importance of the five broad categories of noise that influence any flow model. While some existing literature has already focused on these categories[13,14] we feel they merit more investigation. Perhaps a sensitivity analysis or Monte Carlo simulations could determine which parameters of the distributed model are most affected, thereby focusing PET equipment and acquisition choices to reduce noise. Second, their work raises the general question of what physiologic insights can be gleaned from cardiac perfusion imaging. Computed tomography and magnetic resonance imaging offer superior spatial resolution and perhaps might better investigate the importance of distributed models. Conversely, cardiac PET offers advantages of metabolic targets, almost no tracer contraindications, improved signal-to-noise if

integrative models[15] are used, and coverage of the entire left ventricle with low radiation exposure. The optimal tool should be chosen based on the physiologic question under study.

In conclusion, the dichotomous question in the title of this editorial presents a false choice. Both groups—clinicians and physiologists—model myocardial perfusion but with different goals. For the clinician, such models are just a means to make a treatment decision. For the physiologist, such models are the end result of their mechanistic and structural understanding. Alessio et al[1] remind us that both views are valid and important.

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