LETTERS TO THE EDITOR

Re: Interpretation of Multigated Fourier Functional Images

I suspect that the authors of this paper (*1*) are mixing two basic concepts: one is a model of the kinetics of blood volume in the heart as a periodic single cosine function; the other is the different problem of how to reconstruct a periodic function by a finite number of samples.

The first problem is a physical one; maybe its solution by writing the time behavior of blood volume as a unique cosine function across the whole projected area of the heart volume is too simplistic. Anyway, it provides straightforward correlation between parameters and physiological variables. I agree with the authors that the quantitative correlation leaves a lot of room for improvement. Maybe the cosine function is not the best mathematical expression; maybe the assumption of using a unique function all across the heart image is a poor one (I really think that is the problem).

A completely different problem is: given a collection of time-activity functions, one for each pixel, each one as a finite set of samples, how to find the best numerical fit. This is the problem presented in the referred paper, and the authors present a solution by expanding those functions in a truncated Fourier expansion. The truncation was done by convolution with a modified Hamming window. Obviously, if one looks at the problem from this point of view (a numerical interpolation), the fitting proposed by the authors is a better one than the single cosine interpolation. To prove this you do not require phantom studies and computer simulations.

For this discussion there exist explicit and textbook techniques (*2*) more quantitative and straightforward than the proposed ones. There exist hundreds of options for a solution of this problem, just by trying different windows. The paper does not provide a comparison with these other options, or a criterion to make an optimum selection. The authors observe that four harmonics give a better fit than one harmonic; why not try sixteen harmonics? Is there a convergence phenomenon? What kind of compromise exists between the goodness of the fitting and computation time? What about the number of frames and the Nyquist criterion? This paper provides too many questions and very few answers.

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Reply

We thank Dr. Vergara for his careful attention to our paper (*1*), and for the opportunity to elucidate some points that he has raised.

The paper makes two points regarding "phase analysis" of multigated cardiac studies. One is that the commonly used first-harmonic phase functional image contains information that is contrary to the common view of the first-harmonic phase as representing the onset of contraction. The other point is that by using prior knowledge of the harmonic content of global left-ventricular volume curves (*2*), a more faithful rendering of the pixel time-activity curves is obtained. The multiharmonic representation has the advantage that a number of distinct functional images may be constructed.

The purpose of the phantom studies was simply to illustrate these two points, which are not always made explicit in published discussions of "phase analysis." We do not agree with Dr. Vergara that a first-harmonic fit to the pixel time-activity curve "provides straightforward correlation between parameters and physiological variables."

Dr. Vergara misreads our intentions in finding the central issue of our article to be the optimal fitting of pixel time-activity curves. The main purpose is to clarify the information, particularly images, currently available on almost all commercial nuclear medicine computer systems. These phase images are claimed to represent a parameter like the distribution of the onset of contraction. Our intent was to demonstrate the limitations of this type of interpretation. We advocate the multiharmonic as a way to derive parameters with more straightforward meaning. Regarding Dr. Vergara's other comments, we recognize that processes of the Poisson type are not stationary and, as a consequence, that the Fourier transform is not ideal, since it provides a uniformly weighted least-squares fit. Our modification of the Hamming window reflects a heuristic solution to our concern that the standard Hamming window does not fall off sharply enough. We have not investigated the optimal filter (in part because optimality is a matter of definition) and did not intend readers to infer that we had. The choice of the filter cutoff frequency (or the highest harmonic used) depends on the noise level in the images and on the structures within the field of view of a pixel. The edge of a chamber will produce many higher harmonics as it passes through a pixel. Unfortunately, such an edge will have a relatively low count rate, so it will be relatively noisy. Clearly, an adaptive filter that took this into account would be superior to the stationary one we described in our article. The global left-ventricular volume curve is adequately described by the first four harmonics (*1*, *2*), hence our choice of four. The time-activity curve of a pixel close to the end-diastolic border of a chamber will probably be undersampled, both spatially and temporally. We did not investigate this problem since our aim was to augment the interpretation of multigated studies collected according to established protocols. As a practical matter, we would like to see longer collection times, since the multiharmonic approach is more sensitive to noise. The Orthogonality Principle (*3*) mentioned in our paper describes the convergence of the goodness of fit. The goodness of fit has no consistent effect on the computation times of the multiharmonic functional images.

Again, we thank Dr. Vergara for his comments. We note that our relative generosity with questions reflects the fact that many of them are still topics of research by us and others.

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3. Probability, Random Variables, and Stochastic Processes. Papoulis, A. New York, McGraw-Hill, 1965, pp. 390-490

Dependence of Distribution of Short-Lived Tracers on Decay. A Noncompartmental Approach

In the paper by Modell and Graham (*1*) it was shown that the single-compartment, well-mixed model is a not good predictor of Kr-81m behavior in the lung. The authors tried to explain the differences between the experimental data and theoretical curves generated from a single-compartment, well-mixed model by the inhomogeneity of Kr-81m distribution and its dependence on factors such as combinations of tidal volume and frequency and inspiratory time, but dependence of Kr-81m distribution on decay was not discussed. To assess the dependence of Kr-81m distribution on decay only, one can simplify the problem by considering a system of fixed volume V, where the input concentration is denoted by $I_{in}(t)$, the output concentration by $I_{out}(t)$, the amount of tracer in the system by I(t), constant flow by F, and decay constant by λ. Then

$$I(t) = F \cdot \int_0^t H(t-t')I_{in}(t') \exp[-\lambda(t-t')]dt' \quad (1)$$

$$I_{out}(t) = \int_0^t h(t-t')I_{in}(t') \exp[-\lambda(t-t')]dt' \quad (2)$$

$$(I_{in}(t) = 0 \text{ for } t < 0)$$

Where H(t) is the impulse response function and h(t) is the spectrum of transit times. Equations (1) and (2) may be reduced to the well-known equation

$$\frac{dI(t)}{dt} = F[I_{in}(t) - I_{out}(t)] - \lambda I(t). \quad (3)$$

This, assuming thorough mixing, i.e.:

$$V = \frac{I(t)}{I_{out}(t)}, \quad (4)$$

has been used as a starting point for almost all studies with short-lived tracers. In the case of constant infusion (I_{in} is constant) and the steady state defined by $\dot{I}(t) = 0$, one can combine Eqs. (3) and (4) to write:

$$I = \frac{F}{\frac{F}{V} + \lambda} I_{in}. \quad (5)$$

That is the result for a well-mixed, single-compartment model, as pointed out by Fazio and Jones (*2*). Using a noncompartmental approach [Eqs. (1) and (2)], the ratio between I(t) and $I_{out}(t)$ should be found to obtain a corrected version of Eq. (5),

$$I = \frac{F}{A + \lambda} I_{in}, \quad (6)$$

where,

$$A = \frac{\int_0^\infty e^{-\lambda t}h(t)dt}{\int_0^\infty e^{-\lambda t}H(t)dt}. \quad (7)$$

For long-lived radionuclides ($\lambda = 0$), A^{-1} reduces to

$$A^{-1} = \bar{t} = \frac{V}{F}, \quad (8)$$

where $\bar{t}$ is the mean transit time. In that case Eqs. (4) and (8) are the same, showing that the assumption of thorough mixing is strictly appropriate only in the steady state and with negligible decay. That is, only in such a case is the volume of the system is equal to the volume of distribution of the tracers, which is defined by Eq. (4). For short-lived emitters such as Kr-81m, A may be approximated by $\exp(-\lambda t)$ and the contribution of A may be negligible if λ is large. Hence from Eq. (6) we obtain the approximate relation:

$$I \sim \frac{F}{\lambda} I_{in}, \quad (9)$$

indicating a more nearly linear relationship between the amount of tracer (or concentration at fixed volume) in the organ and the flow for a short-lived tracer than the single-compartment, well-mixed model does.

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Reply

The noncompartmental analysis by Knešaurek represents an alternative mathematical approach to explain our observation that Kr-81m activity compared with ventilation is more nearly linear than is predicted using a well-mixed, single-compartment model. The major differences are in the impulse response function and the spectrum of transit times that are introduced in Knešaurek's Equations (1) and (2). The most reasonable impulse response function for Kr-81m activity in the lung is a simple step function. This would reduce to 1.0 for $t > 0$ and thus would essentially cancel out of Eq. (1). The spectrum of transit times, however, is likely to be a broad function correlating with the general inhomogeneity of ventilation, which, we felt, explained the discrepancy between our data and the single-compartment analysis. This may represent a starting point for a better quantitative approach to the analyses of ventilation inhomogeneity.

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Abnormal Perfusion Scan Due to Intrathoracic Stomach and Colon

There have been previous reports in the literature of perfusion lung scan defects caused by intrathoracic stomach (*1*) and