INVITED COMMENTARY

The Quest for the Perfect Myocardial Perfusion Indicator. . .Still a Long Way to Go

In spite of great strides in developing myocardial perfusion scintigraphy for the last 25 y, the general agreement is that a better radiopharmaceutical tracer needs to be found. In the search for a new perfusion agent applicable to clinical situations, Marshall et al. (*1*), in this issue of *The Journal of Nuclear Medicine*, present results for the compound 7′-*Z*-[^{125}I]iodorotenone (^{125}I-iodorotenone) in the isolated perfused rabbit heart.

Rotenone is a pentacyclic, organic, neutral, lipophilic, and ketonic molecule that is a well-known inhibitor of mitochondrial reduced nicotinamide adenine dinucleotide–ubiquinone reductase, is alleged to bind to complex I of the mitochondrial electron transport chain, and has been extensively used as a tool for investigating structural and functional aspects of that enzyme. Some results (*2*) have been interpreted as indicating that the rotenone-binding site in the mitochondria "recognizes the *whole* molecular structure (or shape) of rotenone in a strict sense [italics in original]." The mitochondrial compartment has been acknowledged to be largely involved in the uptake of ^{201}Tl (*3*) and ^{99m}Tc-sestamibi (*4*) among other tracers. The myocardium is one of the tissues richest in mitochondria.

Enas et al. (*5*) synthesized ^{125}I-iodorotenone analogs and noted that the distribution in healthy mice yielded a preliminary value of more than 25 for the heart-to-blood ratio. As a logical sequence, Marshall et al. (*1*) decided to assay one of the analogs in a stricter and more detailed manner. The method of Marshall et al. can be labeled a typically *biomedical engineering* procedure, so to speak, because it comprises an exacting biologic part and a sophisticated mathematic machinery for the modeling part.

First, the biologic stage consists of collecting the venous effluent from the isolated rabbit heart perfused with a modified Tyrode's solution enriched with bovine erythrocytes and serum albumin. At a selected moment, a bolus of mixed ^{125}I-iodorotenone and ^{99m}Tc-sestamibi as the tracers to be evaluated plus ^{131}I-albumin as an intravascular reference is introduced. The venous effluent in time is counted in a multichannel analyzer that quantifies and records the spectrum from all isotopes in the sample. A variable called the *fractional venous appearance rate*, in general symbolized by h(t), which is a function of blood flow and venous sample radioactivity, is computed.

Second, for studying the blood–tissue exchange of the tracers, the multiple-indicator dilution technique and spectral analysis were used. A crucial assumption in applying the multiple-indicator dilution technique is that the intravascular reference tracer (here, ^{131}I-albumin) accurately quantifies intravascular perfusion tracer transport and dispersion. This quantification is important because, then, any differences between the ^{131}I-albumin venous concentration curve and the curve for radiorotenone or radiosestamibi will "reflect perfusion tracer transit time delays due to movement in and out of the extravascular space" (*1*).

Because the results of Marshall et al. (*1*) are contingent on a powerful mathematic apparatus, some detailed comments on it may be worthwhile. The venous outflow curve for each tracer under investigation reflects the circulatory dispersion, indicated by the curve for ^{131}I-albumin, and the extraction and retention of this tracer by the heart muscle. "To characterize the handling of the tracers by the myocardium in the simplest way, it is desirable to correct the diffusible tracer curves for the circulatory dispersion of the tracer as measured by the albumin curve" (*6*). Recourse is made to a conceptual linear model in which the **d**iffusible tracer curve, $h_D(t)$, is the output of a system with response i(t) to an input $h_R(t)$, which is the albumin tracer curve taken here as **r**eference. In systems engineering terminology, the output $h_D(t)$ is defined as the *convolution* of $h_R(t)$ with i(t) and, bypassing any mathematic notation, can be presented in words as:

Output =

(impulse system response)

CONVOLUTED

WITH (input). Eq. 1

Convolution is shorthand for the definite integral of a product of two functions in time. The process of extracting the impulse response function i(t) from the convolution equation is called *deconvolution*:

System response = (output)

DECONVOLUTED

WITH (input). Eq. 2

If the impulse response function is so emphasized, what is an impulse? We can arrive at a notion of its meaning by considering a rectangular pulse in time (say, in the interval from 0 to t_1) defined in such a way that its area is unity. The height of the pulse will be a

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function of its base, so that the area is constant and independent of the chosen time interval t_1. When one shortens the interval (t_1 approaching 0), the height must increase to keep the area equal to 1.

The impulse function (also referred to as delta function or Dirac delta function and symbolized by δ) is defined as the function that is formed when t_1 approaches 0, so that the time interval becomes 0. The function is 0 everywhere else. To keep the area equal to 1, the height becomes infinity:

$$(\text{height}) \times (\text{base}) = 1 \qquad \text{Eq. 3a}$$

$$(\infty) \times (0) = 1. \qquad \text{Eq. 3b}$$

Intuitively and formally, the expression for the impulse becomes ridiculous from a rigorous mathematic viewpoint and was rejected by the purists for many years, but the expression was given respectability by the solid definition:

$$\int_{-\infty}^{\infty} \delta(t)dt = 1. \qquad \text{Eq. 4}$$

If the impulse function has A units, then it is written:

$$\int_{-\infty}^{\infty} A\ \delta(t)dt = A. \qquad \text{Eq. 5}$$

Of course, such a function cannot be strictly generated in the physical world. However, we can realize that the duration of a pulse can be very short with respect to the time constants of a system, so that from a practical viewpoint a pulse of finite time width appears as if it were a pulse of zero width. A vivid illustration of Equation 3 is the striking of a nail with a hammer (an approximate impulse) versus prolonged pushing of the hammerhead against the head of the nail (a step function or pulse). Much force is obtained with the instantaneous blow, whereas little progress is made by pushing the nail.

The response of a system to an impulse input is called the *impulse system response*, and for a linear system (pragmatically defined as holding superposition of inputs) this response characterizes the system. A palpable, or rather auditory, example is the striking of a gong with a hammer (equivalent to an impulse) and recording of the acoustic answer, which will be the impulse response function for the gong system. By convoluting this response with any other input to the system, one can get the system output for each situation (Eq. 1).

Although the convolution integral has been known for many years, its numeric solution is tedious and did not become useful until the advent of fast computers. But the numeric solution for the deconvolution (Eq. 2)—in fact, an inverse operation—is fraught with enormous difficulties and prone to gross errors. However, under certain constraints such as nonnegative and monotonically decreasing computed solutions, the system response can be estimated.

The convolution (and its more difficult inverse operation, deconvolution), although a rigorous mathematic operation, becomes less robust with variables from the biologic domain because they unavoidably are not "clean" variables—for example, idealizing the tracer bolus as the unrealizable impulse. The uncertainty of the variables is added to the noise, interference, and instrumental error. All combine to distort the output.

In the solution by deconvolution, a spectrum of kinetic components is obtained (*1*) that represents the impulse response function for the two radiotracers under investigation. By combining different components, estimates of extraction fraction, net retention, and washout are derived.

In addition to the tour de force of Marshall et al. (*1*) in obtaining results by deconvolution, the authors were facing the factor that ^{125}I-iodorotenone binds completely to bovine erythrocytes and albumin, which were used in the perfusion fluid, whereas only 25% of ^{99m}Tc-sestamibi is bound. Remarkably, the extraction of ^{125}I-iodorotenone was much higher than that of ^{99m}Tc-sestamibi, revealing that ^{125}I-iodorotenone binding was rapidly reversible.

In summary, the relevant biologic results reported by Marshall et al. (*1*) include the almost doubled average extraction of ^{125}I-iodorotenone compared with ^{99m}Tc-sestamibi; the almost doubled retention of ^{125}I-iodorotenone compared with ^{99m}Tc-sestamibi at 1 min after tracer introduction, and quadrupled retention at 26 min; and the variability in washout rate for one or the other of the radiotracers over time. Although the characteristics of the perfect perfusion indicator—that is, to "be completely extracted and retained by the myocardium so that tissue tracer deposition and myocardial blood flow are directly and linearly proportional" (*1*)—were not met, the results indicate that ^{125}I-iodorotenone is superior to ^{99m}Tc-sestamibi under the given experimental conditions.

Besides the isolated perfused rabbit heart, many techniques can study uptake and retention of tracers in the myocardium, such as the perfused open-chest dog heart, the perfused rat heart, washout from mammalian myocardial fragments, and cultured chick cells. No certainty exists that any tracer shown to yield excellent values in any experimental procedure may show equally excellent results when applied clinically. All sophisticated mathematic models imposed on biologic phenomena harboring tremendous variety always have several malleable assumptions. In this sense, I recognize that Marshall et al. (*1*) have completed a remarkable, ingenious, and useful piece of work, but I cannot share their optimism that the impulse response function "would be equally valid in the in vivo rabbit heart after intravenous tracer injection as is in the in vitro rabbit heart." This possibility remains to be proven experimentally.

Above all else is the species difference. A sobering example is ^{99m}Tc-teboroxime, which showed satisfactory extraction and retention in experimental animals but proved to have shortcomings in patients. How-

ever, comparative studies between two or more tracers using identical experimental conditions—no matter how remote from the clinical scenario—substantially support further investigation of the superior tracer. It is in this context that Marshall et al. (*1*) offer hope for the potential introduction of a new radiopharmaceutical for clinical myocardial perfusion procedures. The authors well recognize the fact that ^{125}I-iodorotenone is unsuitable for clinical use because of the ^{125}I 60-d half-life, but the door is open to labeling rotenone with our good friend ^{123}I (half-life, 13 h) or with the generator-obtained positron-emitting ^{122}I (half-life, 3.5 min). Then, radioiodorotenone may be tested correspondingly in SPECT or PET cameras in medical centers.

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