Editorial: Radionuclide Angiocardiography Revisited

The impending introduction of technetium-labeled myocardial perfusion agents assures the rebirth of interest in radionuclide angiocardiography which is the oldest clinical study in nuclear medicine. Despite its 65 yr of service, this venerable old procedure provides many new contributions to the understanding of cardiac function in patients (*1*). A tracer bolus traverses the complex systems of tubes and pumps within the central circulation in an enormously complicated manner which has defied full mathematical characterization. However, like a jigsaw puzzle of many pieces, placement of each piece enables the easier placement of its neighbor. In like manner, definition of pulsatile and mean pressure and flow interactions progressively converge on a simple solution to the complex flow circuit of the heart. The article by Wu and colleagues points us to yet another window of insight available from this deceptively simple procedure (*2*).

In 1962 Folse and Braunwald were the first to suggest that left ventricular ejection fraction might be characterized from data recorded during transit of a radionuclide bolus (*3*). Attempts to calculate ejection fraction from pulsatile changes in left ventricular counts after left atrial injection of a tracer bolus were thwarted by lack of data processing methodology. Unaware of their work, in 1969 I attempted to refine lung scanning techniques and observed count fluctuations which coincided with systole and diastole in data recorded over the left ventricle during the transit of a radionuclide bolus through the central circulation. The amplitude of these fluctuations was clearly related to cardiac contractility observed on contrast ventriculograms, but accurate left ventricular ejection fractions could not be derived from these count fluctuations. Frustrated by my inability to insightfully analyze these pulsatile data, I nearly memorized the work of Donato et al., describing principles of indicator-dilution theory applied to mean radionuclide angiocardiogram curves (*4*). None of these approaches appeared directly applicable to pulsatile data, and the mathematics necessary to add this additional layer of complexity was beyond my expertise. In desperation, I developed a practical model of the central circulation which enhanced my understanding of pulsatile indicator-dilution theory and to which I continue to return for intuitive proof of relationships whose more formal proofs require mathematics beyond my level of sophistication.

The model is best assembled in the kitchen and requires five cups with 123 white beans and a bag of red beans. Five cups in a row with 20, 8, 70, 20, and 5 white beans represent the relative volumes of the right atrium, right ventricle, lung, left atrium, and left ventricle in end systole (one white bean for each 10 ml of blood). During systole 10 beans move from the right ventricle into the lungs and from the lungs into the left atrial cup. The 10 beans ejected from the left ventricle during systole can be recycled directly to fill the right atrium, thereby bypassing the systemic circuit but conserving beans. During diastole 10 beans from upstream chambers refill ventricular cups.

Thus far the white-bean model has taught us two principles of pulsatile flow important in mathematical modeling of the central circulation. The first important principle is that ventricles can only lose beans in systole and gain beans in diastole. Not every region of the ventricle has to lose beans during systole, but anything that does lose beans during systole is within the ventricle, and anything that gains beans during systole cannot be in the ventricle. These imputable laws persist as long as there is any cardiac ejection and are independent of valve function, intracardiac shunts, or any other pathology. The second principle of pulsatile function is that the exact number of beans ejected by each ventricle is added to some adjacent chamber and in the normal circulation passes into the chamber downstream. A related principle that each ventricle fills with the same number of beans as it ejected during the prior beat is true over any long period of time. However, change in hemodynamic conditions, such as may occur with exercise, shifts blood from the peripheral circulation to the central circulation causing mild increases in cardiac chamber volumes in normal subjects and dramatic changes in patients with left ventricular failure induced by ischemia. A related but more reliable conservation of mass principle would state that the volume of inflow into the central circulation should be nearly equal to the outflow when the heart is at a steady-state condition.

Now we are ready to add an indicator into our pulsatile white-bean model. Red beans will serve as an ideal indicator to trace white-bean flow without adding volume or otherwise perturbing the system. We can introduce all red beans into the right atrium as an impulse or spread the injection over several heartbeats in any bolus configuration desired. As the beans are carefully moved from cup to cup and stirred with each

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beat, the cups progressively turn from white to white and red and back to white, just as a bolus of tracer would sequentially appear and disappear in adjacent cardiac chambers. If by external counting, we could measure all the indicator within isolated cardiac chambers, our models should apply only to the total number of red beans (tracer quantity). If we could float small probes into each cardiac chamber, so that we could detect only radioactivity within a fixed volume sample of blood, typical of all the volume within the chamber, data available would reflect the ratio of red to white beans (tracer concentration). Clinical radionuclide angiocardiography provides data somewhere between these extremes so that we must be concerned with both the total mass of indicator and its concentration within a chamber.

As one begins to move the appropriate number of red and white beans from cup to cup, bolus dispersion adds complexity to the model, as the red beans get scattered throughout the cups by successive washin and washout. Just as individual players in a balloon toss relay race add cumulative delay, the red bean transit through the model is determined by the transfer efficiency of each cup. This transfer function is different for each chamber with a unique volume, but once defined induces a constant permutation on each pulsatile change. Determination of this transfer function for each systole or diastole requires knowing any two of the three controlling parameters:

1. The number of white beans to move (flow),
2. The number of red beans to move (indicator quantity),
3. The ratio of red to white beans to move (indicator concentration).

In clinical practice, it is usually the flow we want to know and the injected indicator quantity and average tracer concentration/time function that we use to derive the absolute volume of flow. However, only relative stroke and end-diastolic volumes are needed for determination of ejection fraction, which, therefore, is independent of the absolute tracer quantity.

If we could accumulate all the spread red beans from upstream chambers into an invisible holding bin, and when all have trickled in, suddenly introduce them into the chamber of interest during a single diastole, we would have a perfect deconvolution of the model. The fraction of red beans ejected from this magically labeled chamber, on the next systole would provide the ejection fraction but not the absolute stroke volume and end-diastolic volume. In the deconvoluted, compressed mode with the right ventricular transfer function expressed using the heartbeat to define time, we intuitively understand the observation of Wu et al. The right ventricle that can transport all red beans with the fewest heartbeats must have the highest ejection fraction.

Having intuitively validated the concept of Wu et al., let us review our experience with the red-bean flow to learn principles of indicator dilution in a pulsatile bean model, which might be used to design mathematical models. The bean model teaches that any mathematical model must deal with bolus spread. Complete deconvolution of all red beans into one cup provides only one pure ejection, and every subsequent ejection spreads red beans by progressive dilution with white beans. Therefore, all practical pulsatile models of the central circulation must describe changes occurring over an adequate number of heartbeats to complete the passage of the tracer bolus through all chambers of interest. Characterization of outflow from one chamber automatically characterizes the inflow to its neighbor. The need for attention to both the mean and pulsatile component of transfer function imposed by the catenary nature of the central circulation is a mixed blessing. The complexity imposed in data processing is offset by the usefulness of interlocking relationships derived from separate principles. This is the importance of the contribution of Wu et al., since a ventricular chamber ejection fraction calculated by pulsatile change in counts from diastole to systole should be the same as that calculated by the mean transfer function described using heart rate as time. These intersections of mean and pulsatile data are joining pieces of the jigsaw puzzle extremely important in the development of models with tightly interlocking pieces. Accurate models of the mean and pulsatile transfer functions of a tracer bolus can be used for practical functions, such as definition of chamber borders based upon temporal separation (5).

Limitations of ejection fraction calculations from mean transfer functions are those intrinsic to radionuclide angiocardiography. Unlike cups of beans, external detection does not completely isolate data from individual cardiac chambers, and some degree of contaminant counts always arises from adjacent chambers because of the complex anatomic configuration of the heart. Other background counts are added by Compton scatter. About 30% of total counts are background, and these change intricately with time. The mean transfer function approach to ejection fraction calculation is as sensitive as any other to the accuracy of background subtraction approaches.

A second potential source of error in ejection fraction measurements from mean flow data relates to the geometry of the heart. In order to enter and leave both the right and left ventricles, red cells must make a "U turn." Moreover, the ventricles are complex geometrically, and trabeculations and irregular surfaces around valve attachments hinder complete mixing within individual heartbeats. This incomplete mixing can be readily appreciated on patient angiographic images of contrast flow through ventricles and has been quantitatively described in experimental animals by Castel-

lana using thermistor probes and cold saline as an indicator (6). Within both ventricles, the net effects of poor mixing from beat to beat is that a greater fraction of the stroke volume originates from the region of the AV valve than at the apex. During the period of increase in concentration of tracer on the leading edge of the bolus, blood entering the ventricle during diastole has a higher tracer amount than the residual blood within the ventricle. The ejection fraction appears inordinately high because ejection of this overconcentrated blood tends to artificially increase ejected counts. During the washout phase of indicator transit, the reverse occurs and the incoming blood contains less tracer than that residing within the ventricle. The ejected blood has a lower than average tracer concentration. Ejection fractions calculated only from the curve upslope are higher than those calculated on the downslope. This changing tracer concentration tends to be self-canceling if the entire function is analyzed, such as was done by the approach of Wu et al., and is an improvement over prior techniques using only tracer clearance rates.

More important, the article of Wu et al. should remind us that the function of the central circulation is that of a circuit with interrelationship of mean and pulsatile events which we can well describe. None of us has fully exploited the information content of these data, and this represents the most important reason to again turn our attention to radionuclide angiocardiography. We should begin by enhancing instrumentation. Nothing new needs to be discovered to introduce gamma cameras with count rates a hundredfold greater than those now available even with the most sensitive multicrystal gamma cameras. Ultra short-lived tracers with half-lives similar to the central circulation time can provide the photon flux necessary to drive the higher counting rate instruments. The small size of these instruments can permit several detectors to be oriented around the chest to view the individual chamber transfer functions from many different directions simultaneously. This not only enhances the total count available from the same dose of tracer, but permits further isolation of each individual cup for bean counting. Those of us sufficiently educated in the mathematics to not need bean models can develop more sophisticated pulsatile models of the central circulation both for decontamination of curves and for full characterization of pulsatile flow and volumes. Completion of this work will fully document the original concept of Blumgart that the height, depth, width, and rate of flow of the river of blood through the central circulation is best traced with radionuclides.

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