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Biventricular Forward and Regurgitant Flows by Radioangiography

TO THE EDITOR: In the paper published in the Journal (*1*) Nusynowitz et al. presented their methodology to assess central circulation kinetics from the first-pass data. More recently the same group reported on clinical aspects in applying their methods (*2*). I wish to comment on several aspects of their work (*1*) that I believe are in error.

In order to calculate biventricular flows they used the Stewart-Hamilton principle (SH) which, applied to the first-pass radioindicator ventricular kinetics, reads (*3,4*):

$$\text{Flow} = \frac{\text{equilibrium count rate} \times \text{blood volume}}{\text{area under the first-pass curve}} \quad (1)$$

In applying Eq. (1) sequentially to the right ventricle (RV), the lungs and the left ventricle (LV), they observe progressive diminution of the flows. They ascribe these downstream flow declines to bolus smearing (in nonregurgitant patients) and to smearing and regurgitation (in regurgitant patients). They further assume that, in absence of right-sided regurgitation, the lung flow equals forward LV flow. Thus they conclude that LV regurgitant flow is the difference in the apparent LV flow, calculated from Eq. (1) using LV area, and the "corrected" LV flow, calculated from Eq. (1) using pulmonary radiohistogram.

The described methodology is ill-posed: the flows obtained utilizing SH principle via Eq. (1) are forward, functional flows, that are invariant to both regurgitation and bolus smearing. I will briefly reestablish these known facts. SH principle relates the indicator concentration at the system output c(t) with indicator output F·c(t). Here F is recognized as the system effective output that carries convectively the indicator particles across the output boundary. Only then the total indicator input (I) is recovered by summing the sequential outputs F c(t):

$$I = F \cdot \int_0^\infty c\,(t)\,dt, \quad (2)$$

which is the formulation of the SH principle. That F in Eq. (2) is the forward flow is widely recognized (*4–7*) and practically utilized (*5–7*) feature. In order that homeostasis is preserved the biventricular forward outputs must be the same and equal to the lung flow, unless there are atrial or ductal shunts. In the absence of shunts unilateral regurgitations cause the difference in the ventricular total: forward+regurgitant flows, the feature widely explored for radionuclide quantitations (*8–11*). The flows calculated from Eq. (1) also do not depend on the tempo of indicator input, that is maybe more obvious by observing that the denominator in Eq. (1) is the product of the total indicator input and the mean residual time of the indicator particles in the ventricular cavity (*12*).

Further, there are two obstacles in applying Eq. (1) to the lung area, as done by Nusynowitz et al. First, in developing Eq. (1) from SH principle one assumes that the radiohistogram generated over the whole system is proportional to the indicator concentration curve at the system output. This may be closely fulfilled for the ventricles, but lungs are hardly close to the perfect mixing model. Second, only part of the lungs is in the background free area, available for the curve generation, whatever projection be used. This further introduces uncertainties in calculating pulmonary flow via Eq. (1).

Finally, Nusynowitz et al. utilized the following relations (*1:Eqs.3,4*):

$$\text{end-diastolic volume} = \text{stroke volume/ejection fraction} \quad (3)$$

$$\text{end-systolic volume} = \text{end-diastolic volume- stroke volume} \quad (4)$$

Equation (3) is correct if both stroke volume and ejection fraction are measured consistently. Nusynowitz et al. calculated the stroke volume from the forward flow F obtained via Eq. (1), while they analysed the first-pass curve oscillations, that gives the total ejection fraction. Thus they underestimated the end-diastolic volumes of their valvular patients. Equations (3 and 4) give:

$$\text{end-systolic volume} = \text{end-diastolic volume} \times (1\text{-ejection fraction}). \quad (5)$$

It follows from Eq. (5) that underestimation of diastolic volume implicates underestimation of systolic volume.

The interaction of the two errors in the paper of Nusynowitz et al.—estimation of LV output using pulmonary radiohistogram and underestimation of LV volumes in valvular patients— may explain for apparent success in correlating radionuclide with catheterization data (*1*) (*Figs. 4, 5, and 6*).

Currently valvular regurgitations can be evaluated by radionuclides using several approaches: biventricular difference in stroke counts obtained from equilibrium (*8,9,10*) or the first-pass study (*11*); comparing the total ventricular flow obtained volumetrically with forward output obtained via SH principle (*5–7*); using pulmonary input deconvolution of radioventriculogram for calculation of forward ejection fraction (*13*), or analysis of the delayed transit time components (*14*).

The methods proposed by Nusynowitz et al. cannot be recommended for evaluation of valvular regurgitations. Instead, the forward outputs of the two ventricles F_{rv} and F_{lv} can be compared to quantitate left-to-right (L-R) shunts. In particular, it holds:

$$\frac{\text{Pulmonary flow}}{\text{Systemic flow}} = \begin{cases} F_{rv}/\ F_{lv} \text{ in ASD} \\ F_{lv}/\ F_{rv} \text{ in PDA} \end{cases}, \qquad (6)$$

because in L-R shunting due to ASD the shunt flow avoids LV, but goes through the RV, contrary then in L-R ductal shunts.

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REPLY: Eterović apparently misinterpreted our equations. He commented that "... they concluded that LV regurgitant flow is the difference in the apparent LV flow... and the 'corrected LV flow' ...". In fact, we stated that regurgitant flow is the difference between the pulmonary flow and the apparent (uncorrected) LV flow.

Eterović asserts that indicator dilution flows are forward flows and are invariant to both regurgitation and bolus smearing. We disagree. Regurgitation can be viewed mathematically as a negative feedback, or as Lassen and Perl describe it, as "instant recirculation" (*2*). If one assumes monoexponential washout of indicator from a nonregurgitant LV, it can readily be shown that the effect of regurgitant flow (feedback) is to decrease the rate at which indicator leaves the LV. This slower rate translates into an indicator dilution curve downslope that is shallower than for the nonregurgitant case, and in turn the shallower downslope leads to an increased area under the indicator dilution curve. Since this area is in the denominator of the cardiac output equation (Eq. 1, Ref. 1), the increased area due to regurgitation leads to a decreased cardiac output; this decreased cardiac output is exactly in accord with our clinical observations.

Lassen and Perl (*3*) deal with the issue of bolus smearing in exacting mathematic detail. Briefly, note that, in Eq. (1) (*1*), the ratio of Ceq to the area under the curve is the reciprocal of the mean transit time. The total mean transit time represented by this term is the sum of the mean transit time of the system under consideration (LV, RV, or lungs) plus the mean transit time of the "injection". In the case of the RV, the bolus is very tight and the injection component is small. However, by the time the "bolus" has arrived in the LV, it has been smeared by the mean transit times of the RV and lungs. This smearing results in a much increased "injection" mean transit time as input into the LV and leads ultimately to an increased area under the indicator dilution curve. Convolution analysis has been proposed to deal with this effect, as suggested by Eterović's Ref. 13, but to date this type of analysis has been difficult to implement and has not lead to widely accepted improvement in data analysis. Thus, we disagree that flows calculated from this ratio (Ceq/Area) do not depend on "tempo of indicator input".

We agree that the lungs are not a perfect mixing model and that the entire volume of both lungs cannot be included in our regions of interest. However, we use as large a portion of the lungs as possible and we rely on the "convective spaghetti model" and bolus fractionation principle as described by Lassen and Perl (*4*), which states that the flow through a fraction of a larger volume is proportional to the flow through the entire volume if the various flow channels carry approximately equal flow. This is clearly an assumption that cannot be proved or disproved; we feel confident in making the assumption given the excellent correlations we observed (*1*).

Eterović has also misinterpreted our description of how we calculated EDV. We do *not* use forward flow. We use corrected (total) LV flow (forward plus regurgitant) to calculate SV and we use total (forward plus regurgitant) flow to calculate EF; thus, we are consistent. Eterović also asserts that F in his Eq. (2) is "widely recognized" as forward flow. We agree, so long as there is no regurgitation or shunting, or other process that might mimic them (e.g., bolus smearing).

Since we did not actually make the two errors suggested by