If EDC(i) is the left ventricular (LV) count rate at i-th end-diastole following the bolus arrival and LVEF, then, according to Green et al. (1), the total indicator dose is given by:

$$\text{dose} = \text{LVEF}\cdot(\text{ECD}(1) + \text{EDC}(2) + \text{EDC}(3) + \ldots\ldots). \qquad \text{Eq. 1}$$

The above equation was derived after some preliminary calculations. It referred to the ideal case when the transit of indicator bolus is completed before the onset of systemic recirculation. The authors then state without proof that the relationship still holds during LV regurgitation, but then LVEF denotes the forward component of total the LVEF. They also imposed the constraint that regurgitant activity originating from each systole fully returns to the ventricle in the subsequent diastole. The latter implicates that in instances of mitral valve insufficiency, due to fractional reinputs of each regurgitant activity from the left atrium, Equation 1 is not exactly valid.

The above relationship, however, can be obtained much more directly and in a more general form to allow for eventual valve insufficiency, irrespective of its site.

To verify this, observe that LVEF·EDC(i) is simply the i-th LV indicator output. By neglecting systemic recirculation, the sum of all sequential LV outputs equals the total indicator dose. In instances of LV regurgitation, the total indicator dose is recovered by summing the parts of LV outputs that irreversibly leave the left ventricle via the aorta, or eventual septal defect. Clearly, LVEF in Equation 1 is the forward component of the total LVEF, which is equally valid for mitral and aortic regurgitation.

Atrial smearing of the regurgitant indicator in mitral valve insufficiency poses additional problems in some deconvolution analyses of first-pass indicator histograms, which are not present in aortic regurgitation (*2*, *3*), but it does not violate Equation 1. The only obstacle to validating Equation 1 is right-to-left ventricular shunting. This would affect LVEF·EDC(i), in that only a portion of LV it-h output, i.e., that part which originated from the previous diastolic input, would be represented. Systolic input to the left ventricle from the right ventricle is the other part of LV single-beat output.

The methodological difference between the two approaches is that Green et al. considered sequential inputs in the left ventricle, whereas we featured consecutive indicator outputs. The advantages of the latter are obvious.

Still, the reader may find valuable information in the relationships that Green et al. utilized in arriving at Equation 1. For example, the following recursive relationship (*1*, see Appendix):

$$\text{EDC}(i + 1) = (1 - \text{LVEF})\cdot\text{EDC}(i) + \text{i-th diastolic input to LV}$$

can be used to calculate LVEF from pulmonary and LV indicator first-pass curves (*3*).

Finally, we would like to point out that a mere statistical comparison between first-pass and equilibrium gated methods underestimates the overall performance of the former. This is particularly true because of the lower background level typically present in the first-pass studies. Since background subtraction only imitates the true background activity, which is not known, the result of this maneuver would greatly affect the accuracy of the output parameters of the equilibrium study. Thus, both precision and accuracy of the study results should be considered when comparing the two methods.

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REPLY: In our paper (*1*), we derived an expression for total cumulative left ventricular (LV) end-diastolic activity when a tracer dose Q passes once and only once through the left ventricle and no ejected activity reenters the ventricle by regurgitation:

$$\text{Total cumulative LV end-diastolic activity} = Q/EF, \qquad \text{Eq. 1}$$

where EF is the total ejection fraction. At the end of the Appendix to our work, we stated, but did not prove, that when regurgitation is present, Equation 1 should be modified by replacing the total EF with the forward ejection fraction, EF_f. Thus, both we and Dr. Eterović agree that the correct expression for the general, regurgitant case is:

$$\text{Total cumulative LV end-diastolic activity} = Q/EF_f. \qquad \text{Eq. 2}$$

At the end of the Appendix, however, we stated that for this expression to be true, a constant fraction of ventricular activity at the beginning of a given beat must reappear as input to the ventricle during diastole of the same beat. We introduced this requirement to allow certain simplifications in the method that we used to derive Equation 2. Dr. Eterović's comments have spurred us to re-examine this method of derivation and, hence, the need for this constraint. Although the results of our analysis are correct, it is true, as Dr. Eterović suggests, that the constraint is unnecessary. All that is required is that all of the regurgitated activity eventually pass through and out of the ventricle. The way in which this activity is regurgitated is not important. In our original paper, we did not treat the regurgitant case at length because it was not central to the issues we addressed in the paper, namely how the first-pass and gated equilibrium methods compare when some objective and intrinsic criteria are used as the basis for comparison. Dr. Eterović's remarks suggest, however, that it would be useful to explicitly derive the general expression for total cumulative LV end-diastolic activity when regurgitation is present. We do so below.

Imagine a ventricle without regurgitation. After passage of a tracer bolus of magnitude Q through the ventricle, the cumulative LV end-diastolic activity will be, by Equation 1:

$$Q/EF.$$

If no regurgitation is present, as we have assumed, this will be the final value for total cumulative activity. On the other hand, imagine that some fraction of this cumulative activity is re-cycled through the ventricle again because of regurgitation. By definition, this fraction will be the regurgitant fraction, EF_r, so that the fraction of this cumulative activity recycled will be:

$$(Q/EF)EF_r$$

and, after complete passage of this fraction of activity through the ventricle, add the amount:

$$((Q/EF)EF_r)/EF = Q(EF_r/EF^2)$$

to the growing total LV cumulative activity. A fraction EF_r of this cumulative activity will, in turn, be recycled through the LV as regurgitated activity and this fraction will contribute to the growing total cumulative activity in the amount:

$$Q(EF_r^2/EF^3).$$

Thus, after three transits, the cumulative LV end-diastolic activity will be the sum of these three terms:

$$Q/EF + Q(EF_r/EF^2) + Q(EF_r^2/EF^3) \ldots\ldots$$

Re-arranging gives:

$$(Q/EF)(1 + (EF_r/EF) + (EF_r/EF)^2 + \ldots\ldots).$$

It is clear that if we allow all regurgitated activity to wash out from the LV by repeated passages through the LV, more and more terms will be added to this series. The resulting series has the form $1 + X + X^2 + X^3 + \ldots\ldots$ where $X = EF_r/EF$. This series converges to the sum $1/(1 - X)$. Thus, total cumulative LV end-diastolic activity when regurgitation is present is:

$$(Q/EF)(1/(1 - (EF_r/EF))).$$

Since $EF = EF_r + EF_f$, where EF_f is the forward ejection fraction, this expression reduces to:

$$(Q/EF)(EF/EF_f) = Q/EF_f.$$

Thus,

Total cumulative LV end-diastolic activity $= Q/EF_f$.

It is important to note that in this derivation we have assumed nothing about the beat-to-beat distribution of tracer, only that all regurgitated activity eventually passes through and out of the LV into the systemic circulation. Thus, our constraint requiring a particular intra-beat distribution of activity is unnecessary. We obtained the "right" answer with our original unreported derivation because the constraint we imposed was one of many (valid) ways in which activity can pass through, and out of, the ventricle by regurgitation. The derivation above requires only that the ventricle eject blood (the total EF) and that a constant fraction of this ejected blood flows eventually back to the ventricle as input. This relationship holds, as noted by Dr. Eterović, for both mitral and aortic regurgitation. Finally, Dr. Eterović implies that summation of ventricular outputs is in some sense advantageous compared to our approach of summing ventricular inputs. The derivation above is based on summation of ventricular inputs and yields the same result obtained by Dr. Eterović. The advantages of one approach over the other are, in our view, not particularly compelling since both approaches are physically equivalent.

Dr. Eterović next suggests that several of the equations derived in our article might find other uses. We agree, particularly with respect to Equation 2, above. According to this equation, we could, in principle, compute the forward ejection fraction from a single, composite, background-corrected end-diastolic image acquired during the full bolus passage if we could correct the cumulative LV activity for attenuation. Several methods for making this correction have been reported so that it may be possible to use Equation 2 for this purpose. Comparison of the forward ejection fraction with the total ejection fraction obtained by analyzing the "representative cycle" in the usual manner might thus provide a potential method for detecting and quantifying the presence of valvular regurgitation. This conjecture would, of course, have to be proven by experiment since many assumptions, including the presumed absence of recirculation, underlie the derivation and interpretation of Equation 2.

Dr. Eterović concludes his remarks by stating that he believes the first-pass method to be judged unfairly in our paper because we do not include accuracy as one of the comparison criterion. We did not include accuracy or any other methodological conditions in our comparison for several reasons. First, an abundant literature supports the view that, in practice, both methods yield reasonably accurate estimates of systolic LV function irrespective of background differences. Second, as we stated in our paper, our intent was to compare the methods using a wholly objective criterion. Accuracy depends not only on differences in background but on the validity of all of the assumptions that underlie both methods, on the specific methodology used to make the necessary measurements, i.e., method for defining the necessary ROIs, etc., on the imaging device and on many other factors, none of which lend themselves to unambiguous (or unbiased) quantification. By comparing the statistical precision of the two methods, we avoided all such ambiguities and produced what we believe to be a reasonable, as well as fundamental, comparison of the methods. Since Dr. Eterović addresses the matter of "fairness", however, we should point out that our objective method of comparison is actually biased in favor of the first-pass method and gives "equivalence times" that are longer than they probably are in practice. Recirculation will inevitably cut off observation of the bolus transit so that the total counts accumulated in a first-pass study will always be less than we have calculated. If anything, we have treated the gated equilibrium method "unfairly" rather than the other way around.

Despite these few differences, we interpret Dr. Eterović's remarks as largely in agreement with our findings. We thank him for pointing out that the constraint we thought necessary in deriving Equation 2 is, in fact, unnecessary and for providing us with an opportunity to clarify and further amplify on our original work.

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