EDITORIAL

Whither Water?

In the preceding pages, Herrero and colleagues (*1*) have pointed out a rather large error which can occur when using the bolus $H_2{}^{15}O$ method for measuring myocardial blood flow. This error is caused, surprisingly, by the small, 1-sec time delay which occurs between the arrival of the arterial input function measured from the left atrium, and the actual arrival of activity in the myocardium.

The effects of arterial time delay on blood flow have been examined in the past by other investigators (*2–4*) who were interested in the measurement of cerebral, rather than myocardial, blood flow. With brain imaging, of course, there is no structure equivalent to the large left ventricular (LV) or atrial (LA) chambers from which one can make a direct PET measurement of the arterial input function. Instead, actual arterial samples of blood had to be withdrawn and counted from a catheter in the radial artery. This introduced both dispersion and time shift between the arterial activity concentration of blood entering the brain determined from the blood samples. Studies indicated that if unaccounted for, a time delay in the arterially sampled blood would cause an artefactual increase in calculated flow (*2*). Researchers also realized that even if one was able to accurately shift the measured arterial curve to the "true" value (e.g., to the value which would be obtained if one were able to measure, for example, the internal carotid artery concentration), different regions of the brain would receive blood earlier or later than other regions (*4*).

Computer simulations and experiments predicted that a 3-sec arterial delay could cause as much as a 12% error in flow, depending on how the data were acquired and analyzed (*2*). Despite (or perhaps because of) this body of work, the effect of time delays on the measurement of cardiac blood flow were ignored. Cardiac imaging allowed direct measurement of the arterial-input curve at locations quite close to the vessels supplying the myocardium. The time shifts were therefore presumed to be negligibly short. Indeed, in Herrero's paper, the mean-time delay from the furthest point that one might sample (the left atrium) to the aorta was on average only about 1 sec. How then, does one explain Herrero et al. finding such large biases in flow? The authors find that flows at rest changed from 1.28 ml/min/g when data were uncorrected for the one-sec time offset, to 0.98 ml/min/g after the correction was made—nearly a 30% change. This is a much larger error than one might predict based on studies in the brain. A clue comes from Herrero et al.'s observation that they, like other workers, usually only analyzed the first 90 sec of data. This seems reasonable at first, since brain blood flow studies have shown that it is the early data that contains most of the useful flow information. However, when Herrero investigated four patients with longer acquisitions, she found that extending the analysis from 90 sec to 5.5 min reduced the presumed bias caused by the time shift from 26% to 11%. This suggests that the late data is perhaps more important for cardiac studies than one might think. The reasons for this become clear if one examines first how the data are analyzed and second how the data look in both brain and cardiac studies.

There is a small but fundamental difference in the way brain and cardiac data are analyzed. Herrero et al., like many other researchers using ^{15}O-water to measure myocardial flow, include a partial volume correction term (called F_{mm} in Herrero's paper) in the model (*5*). This is an important term, because it corrects for variations in wall thickness and thickening and for variations in the way the myocardial regions of interest are drawn. In the brain model, which uses no such correction term, it is flow which multiplies the convolution term in the model, while in the cardiac model it is the product of flow and F_{mm}. This difference causes most of the flow information in cardiac data to come from the late portion of the curve—the efflux phase, while for the brain it comes from early times—the influx phase. In addition, the myocardial tissue curves have one striking feature which distinguishes them from brain tissue curves. As the bolus passes through the heart, the concentration of activity in the left ventricular cavity is exceptionally high, resulting in the well known "spill-over" of counts from the LV cavity into regions of interest drawn around the myocardium. Spill-over is caused by the finite resolution of the scanner, as well as the effects of wall motion. Spill-over is accounted for by including a spill-over term in the model—i.e., by assuming that the measured myocardial activity will be the sum of the true myocardial activity plus a fraction of the arterial concentration (i.e., the concentration of blood in the left atrial cavity). A similar phenomenon occurs in the brain, but to a far lesser extent, due to contamination of supposedly pure "brain tissue" regions of interest by the presence of arterial blood (*2*). In the heart, however, this is a huge effect. Herrero et al. find that nearly 30% of the arterial-concentration curve spills over into the myocardial data. In contrast, contamination of brain tissue by arterial blood is thought to be at least 10 to 30 fold less. This means that in myocardial time-activity curves, the initial data has little or nothing to do with myocardial blood flow, but rather is dominated by contamination from the LV cavity. The very portion of the data which yields the bulk of the flow

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information in the brain—the early influx phase—is overwhelmed by the spill-over. It now becomes clear why cardiac flow values are so sensitive to timing errors in the arterial curve. The myocardial time-activity curve consists of a large, sharp, early peak, followed by a much more slowly changing washout. When such data are fitted to the sum of an (erroneously delayed) arterial curve fraction and the usual slow exponential convolution term, fitting will be dominated by the sharp early peak. If this sharp early peak (the spill-over) is at the wrong time, it will force the entire slowly changing clearance part of the curve (the only part remaining which contains flow information) to be in error. This is presumably the reason why using longer (5 min) data sampling reduced the apparent flow bias due to time shifts. The more data at the end of the curve, the less will be the influence of the (erroneously delayed) early part of the curve in the fitting process. Presumably, the flow bias due to delay will also be strongly dependent on the magnitude of the spill-over fraction (and therefore on exactly how the myocardial ROIs are drawn), but this remains to be proven. Another factor which may strongly influence the degree to which time delays affect flow is the poor count rate performance of most PET scanners. The severe dead time and randoms which occur as the bolus passes through the cardiac chambers increases the statistical noise of the early data. If one properly fits the data to the model, these early data will therefore be given less weight than they would otherwise, making flow a little less sensitive to the time shift than it might otherwise be. Conversely, if one does not do a careful job of computing the weighting factors, an artificially increased sensitivity of flow to arterial time delay may result.

Oxygen-15-water has many advantages as a flow agent; it has high extraction fraction, it is freely diffusable, and it is not confounded by metabolic effects. Unfortunately, the poor count-rate performance of most PET scanners severely limits the use of ^{15}O water for measurement of cardiac blood flow. Because of this, the activity which it is possible to inject for cardiac imaging is limited not by dosimetry considerations, but by the ability of the PET camera to handle the high count rate as the bolus passes through the heart. Thus cardiac injected activities are many times lower than those used in brain imaging. This lower injected activity results in high statistical noise and correspondingly high standard deviations of regional flow. Standard deviations of 20% are common even for large myocardial ROIs in the normal myocardium and still larger percent errors in flow are encountered at low flows. Such large standard deviations have made researchers consider switching to other flow agents. Should Herrero's evidence of significant bias in flow with even miniscule arterial time delays be "the straw that breaks the camel's back," causing us to give up water as a cardiac flow agent? Probably not. Herrero et al.'s paper suggests that while aortic ROIs may not be suitable for determination of the arterial input function, the curves from such regions would allow accurate prediction of the time offset. Herrero et al. believe that the aorta is preferable to the LV cavity for this determination, since the former is most temporally aligned to the myocardial tissue. However, as suggested above, the principal cause of the flow bias may be temporal offset between the measured (LA) arterial curve and the spill-over portion of the myocardial curve, not the offset between the LA and the activity arrival in the myocardium. If this is indeed true, then perhaps the LV might actually be better than the aorta for determining time delay, since the LV time activity curve is in absolute synchronization with the spill-over portion of the myocardial time-activity curve. In any case, although Herrero et al. have pointed out a significant source of error in the use of water as a cardiac flow agent, it seems that a correction for this error may be possible. One suspects, therefore, that noise caused by low-dose and poor scanner performance will continue to be the limiting factors in the use of water as an accurate myocardial flow agent.

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