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What Is the Meaning of *Quantitative CBF*?

Proponents of MR imaging, CT with iodine, xenon CT, positron emission tomography (PET), sonography, and soon-to-be-available optical modalities often claim that these techniques quantitate CBF. Vendors provide software and hardware to create images that they claim represent CBF, and increasingly, these vendors attach scale bars with numbers on them. In particular, there seems to be something magical when the vendor can promise ''absolute CBF'' in mL/100 g/min. Often, articles, such as the one authored by Kikuchi et al in this issue of the *AJNR* (page 248), indicate that the method being described has this ability to provide absolute quantitation. How might neuroradiologists view such a claim?

Certainly, true quantitation of CBF might well be of tremendous clinical value. Animal and some human data seem to indicate that in the case of acute cerebral ischemia, the level and duration of the ischemia are critical in determining tissue outcome after an ischemic event. There are suggestions that cerebrovascular reserve, or how much reserve blood flow might be available on demand, could be a useful measure for predicting which patients might go on to infarction in the future. As a result, the quest for quantitative imaging seems to be quite valid.

I, however, believe that there is more to quantitation than simply placing numbers on the scale bar next to the images that an instrument scanner produces. I would like to suggest a key issue that consumers of these data might consider when judging these new methodologies: error bars. In biological studies, all measurements have some uncertainty or variance associated with them. Therefore, any measure of CBF should have associated with it some way of estimating how well the flow is actually known, or some indication of the error bar size. Error bars represent variance from a number of sources, including:

1) *Reproducibility.* If a flow measurement is obtained, and then the patient is taken out of the instrument, put back in, and another flow measurement obtained, how different will the two measurements be? Just as a good bathroom scale might differ slightly in its measurements if one steps off and steps back on, we expect some variation as measurements are repeated. A good scale is one wherein the variation is minimal; but to claim zero variation is to imply that one does not understand how measurements are made.

2) *Robustness.* What happens to the reported measurement if the experimental conditions are modified slightly? Two examples arise. In the first example, with PET and many other techniques, quantitation is often achieved by obtaining the arterial input function from the radial artery, and the assumption is made that this represents the arterial input function to the brain. But what if the patient has unilateral carotid stenosis? In such cases, the radial arterial input function (AIF) no longer can be assumed to be the carotid AIF. Most PET models allow further assumptions to be made in such cases, but these are assumptions that may or may not be valid in any given patient. In a second example, in imaging with contrast perfusion MR, the degree of signal change in a tube (like the middle cerebral artery) changes with the orientation of the tube to the static magnetic field. This means that if a patient turns her head 30 degrees from one examination to another, the AIF will change, possibly quite dramatically. How does such a change in the AIF change the measurement of flow? Answers to these questions should be available before one puts too much faith in a particular ''quantitative'' technique.

3) *Range.* Many techniques including PET, arterial spin labeling, and most tracer kinetic approaches make assumptions in their attempt to quantitate flow. Unfortunately, often these assumptions become less valid in exactly the pathologic states in which flow quantitation is most important; namely, when flow is very low. Therefore, some sense of the size of the error bars not only in healthy volunteers but also in patients with pathologic conditions is crucial.

4) *Calibration.* Frequently one discovers that quantitation is obtained by assuming normal flow and then choosing scale factors to let gray and white matter have values that are thought to be in the normal range. Although this may be a reasonable approach in population studies of healthy volunteers, it is, in essence, an outright assumption, not a calibration technique. Indeed, calibration is not easy because there are so few standards of reference, and the methodology that appears to work in one setting often may not be reproducible in other settings (1). Learning how the manufacturer or purveyor of the technique has chosen to perform the calibration, if calibration is performed at all, will often help one understand the nature of the error bars.

Often there are no error bars, and one must make these estimates directly. How might this be done? This may be a matter of experience. When I look at images and see flow in places it doesn't belong (ie, positive CBF in the ventricles or skull), lack of flow in the white matter as in the ventricles, or large artifacts, I can estimate the ''error bars'' mentally, even if the vendor has not supplied them.

It is important, of course, to avoid focusing on error bars, thereby obscuring the value that the perfusion data can provide. Many neuroradiologists have found perfusion maps to be highly valuable

in most clinical settings, even as a relative map. (*Relative* here means that if the maps show double the flow in one area, this truly represents a doubling of flow, but does not allow one to assign actual flow rates to a given voxel). It appears that qualitative approaches are adequate in assisting in the diagnosis and management of many diseases including stroke, brain tumors, and cerebrovascular reserve. Furthermore, the few studies that have looked at quantitative or semiquantitative measures of blood flow in humans document that there is not the same tight correlation between blood flow defects and infarctions in humans that there is in animals (2). This is almost certainly in part because all of our current imaging techniques provide a snapshot in time; this works fine for carefully controlled animal models but does not seem adequate to capture the range of human pathophysiological processes. Such lack of correlation argues that the quest for absolute quantitation, while scientifically important, may not yet be clinically relevant, at least not while our instruments are not continuously monitoring blood flow at the bedside.

In summary, I believe the ongoing efforts to quantitate blood flow should be encouraged and applauded, but we ought to be realistic about the difficulties of the task, and be wise consumers of these data. Furthermore, we should realize that we do not need to let the ongoing lack of a truly quantitative, accurate, robust method preclude us from helping our patients by using perfusion imaging in whatever form we find available and convenient.

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