EDITORIAL COMMENT

Placing Faith in Numbers: Quantification of Perfusion With Myocardial Contrast Echocardiography*

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Clinical decisions in cardiology are increasingly being based on absolute measurements of chamber size, left ventricular (LV) performance and valve area. Accordingly, quantification has become an integral part of echocardiography. A relatively new application for echocardiography is the assessment of myocardial perfusion with myocardial contrast echocardiography (MCE). This technique relies on the acoustic detection of microbubble contrast agents as they transit the microcirculation within the ultrasound beam. Detection of coronary stenosis and myocardial viability with MCE in patients has relied largely on subjective interpretation of regional perfusion by experienced readers rather than using quantitative techniques. Similar to radionuclide perfusion imaging, where interpretation has been facilitated by quantification of single photon emission computed tomography (SPECT) information (1,2), quantification of MCE data will likely be necessary for its routine application. The evaluation of perfusion with MCE relies on measuring the product of microvascular blood volume and microvascular blood velocity (3). In this issue of the Journal, two separate groups describe their experience with relatively new methods for quantifying or displaying these parameters (4,5). A critical analysis of the merits and limitations of these studies sheds light on our expectations from computerized quantification and how we can avoid evaluation caused by tissue and for depth-dependent scatter (9).

One of the criteria by which we identify a reader as an "expert" in myocardial perfusion imaging is his or her ability to distinguish artifacts from actual perfusion defects. Quantification can reduce the influence of artifacts by several means. First, computerized quantification can be used to establish a database to be used as a normal standard to correct for commonly encountered artifacts. For example, radionuclide imaging quantification programs have been developed that use statistical variation of regional scintigraphic intensity based on body habitus and gender to help the reader identify attenuation artifacts (1). Methods have also been developed for radionuclide imaging whereby computer analysis can numerically correct for signal attenuation caused by tissue and for depth-dependent scatter (9).

Beside enhancing diagnostic accuracy, a secondary role of quantification in non-invasive imaging is to measure a meaningful parameter that influences clinical decisions. For example, quantitative measurements of radionuclide tracer uptake or positron emission tomography metabolic tracers have been used to indicate the degree of myocardial viability. Thresholds have been established whereby the segmental or global recovery of systolic function can be predicted (10). For the assessment of myocardial perfusion, absolute quantification in terms of flow per muscle mass remains an unmet goal and would improve detection of multivessel disease, quantification of stenosis severity (by measuring flow reserve), and assessment of viability.

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**Goals of Quantification**

The primary reason for the routine use of quantification in cardiac imaging is that it improves reproducibility and, sometimes accuracy, of interpretation. For myocardial perfusion imaging, quantification can have a positive effect on many of the variables that influence interpretation, such as reader expertise, reader bias, and imaging artifacts. Irrespective of the non-invasive imaging technique used, there is interobserver variability that can be explained by different levels of experience or expertise. Disagreement in interpretation can occur even between experienced readers and is often due to how imaging artifacts are handled. For lack of better terms, the interpreter must assume a certain position on a receiver-operator curve. For example, some readers have a relatively low threshold for calling an abnormality a perfusion defect, in which case their sensitivity will be high at some expense to specificity and positive predictive value (or "over-callers," in less-flattering terms). Other readers may have a much higher threshold for calling an abnormality a true perfusion defect, in which case specificity and positive predictive value will be better, but sensitivity will be lower ("under-callers"). Although there are no perfect readers, quantification of non-invasive imaging information has the potential to improve both accuracy and uniformity of interpretation of myocardial perfusion (1,6). For echocardiography, quantification protocols based on border detection or myocardial shortening velocities have been developed and tested that can improve accuracy and uniformity in evaluating systolic function (7,8).

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Beside enhancing diagnostic accuracy, a secondary role of quantification in non-invasive imaging is to measure a meaningful parameter that influences clinical decisions. For example, quantitative measurements of radionuclide tracer uptake or positron emission tomography metabolic tracers have been used to indicate the degree of myocardial viability. Thresholds have been established whereby the segmental or global recovery of systolic function can be predicted (10). For the assessment of myocardial perfusion, absolute quantification in terms of flow per muscle mass remains an unmet goal and would improve detection of multivessel disease, quantification of stenosis severity (by measuring flow reserve), and assessment of viability.
Perfusion imaging with MCE is unique in both the information it yields and the method by which this information is acquired. Myocardial contrast echocardiography is performed with intravenous administration of encapsulated microbubble contrast agents. These microbubbles remain within the vascular compartment and behave similar to red blood cells in the microcirculation, where they are imaged (11). At a time when the microbubble concentration in the blood pool is relatively constant, microbubbles within the acoustic beam are destroyed by high-power ultrasound. The rate and extent of microbubble replenishment within the beam, measured by acoustic enhancement, provide information on microvascular blood velocity and blood volume, respectively (3).

To date, most studies using MCE to assess regional perfusion or viability have relied on subjective interpretation of MCE images, which has several limitations. The first is the inherent difficulty in visually identifying regional differences in the velocity parameter from movie clips or a series of frames. Second, there are many imaging artifacts that can produce regional heterogeneity in contrast enhancement: for example, attenuation from microbubbles in the LV cavity, where their concentration is 10- to 20-fold higher than in the myocardium. Finally, despite recent advances in phased-array transducer technology, there is still substantial heterogeneity of power in the acoustic field. This produces heterogeneity in contrast-enhancement, depending on the location of microbubbles in the acoustic beam and on the position of the acoustic focus. Attenuation and power heterogeneity affect primarily the blood volume parameter on MCE imaging. Although quantification is potentially useful in avoiding these problems, absolute quantification of MCE data has been performed in few clinical studies (12,13).

ADVANCES OF THE RECENT STUDIES

In the study by Yano et al. (4) in this issue of the Journal, the authors investigated the merits of a method for quantifying microvascular blood volume on MCE. They derived an index of microvascular blood volume fraction in the myocardium by comparing myocardial signal intensity to that in the blood pool immediately adjacent in the LV cavity. Because acoustic intensity was measured in log-compressed values, the blood volume fraction (in relative units of dB) was calculated by subtracting myocardial intensity from LV cavity intensity. This algorithm was designed to correct for far-field signal attenuation caused by tissue and to normalize for heterogeneity in the acoustic power. As a result, spatial heterogeneity from poor signal in the basal and lateral segments was reduced, but not eliminated, in normal subjects. Using this technique, the authors also were able to correct for temporal heterogeneity in signal intensity caused by a gradual decline in microbubble concentration that occurs after a bolus injection.

The incremental diagnostic value of quantifying microvascular blood volume is implied but not tested in the study by Yano et al. (4). By correcting for attenuation, power heterogeneity, and temporal variation in microbubble concentration, it should be possible to differentiate perfusion defects from artifacts and to more accurately assess regional perfusion. To determine whether the measurement of blood volume fraction provides a meaningful measure of viability, the investigators measured myocardial blood volume index in patients with previous infarction. Their index of blood volume fraction was accurate for identifying segments where wall motion would recover. Analysis of uncorrected data was less predictive. These results should be interpreted with caution because only endocardial blood volume fraction was quantified. Resting wall motion is largely dependent upon the status of the endocardium (14). It cannot be inferred that this technique is a suitable indicator of transmural viability for prediction of long-term outcomes, symptoms, and susceptibility to adverse remodeling. Other MCE studies have demonstrated that substantial viability often is present in segments that are akinetic at rest but possess contractile reserve (15,16). Further experience with this strategy is needed to determine whether transmural correction is possible.

The study by Yu et al. (5), also in this issue of the Journal, examines the use of commercially produced software that displays the parameters of microvascular blood volume and velocity and their product in color-coded formats. Parametric imaging for MCE was first described by our laboratory five years ago in a study designed to test whether transmural differences in perfusion could be better represented (17). The impact of the current study is substantially limited because parametric imaging does not, per se, provide any additional quantitative information on perfusion. Instead, it is a means of display and relies on subjective analysis of patterns. Parametric imaging in its current form does not, as suggested, reduce the “tedious” tasks of quantification, because it still requires image selection, alignment, and identification of borders.

Parametric display has been particularly helpful for spatially characterizing abnormalities in microvascular velocity and blood volume that occur in association with tumor angiogenesis (18). For myocardial perfusion imaging, this technique could similarly be helpful in spatially measuring flow abnormalities and identifying attenuation artifacts that affect primarily microvascular blood volume but not blood velocity values. It also has the advantage of providing a single image for evaluating the microvascular blood velocity parameter. For detecting the presence of perfusion defects, we would expect a small impact from parametric imaging, such as the visual identification of mild or subendocardial perfusion defects. It is, therefore, not surprising that Yu et al. (5) found only a very modest increase in the correlation between MCE and radionuclide SPECT imaging with parametric display. Moreover, the investigators did not use optimal qualitative methods to assess perfusion visually. Full
video clips rather than end-systolic data were viewed, which can affect relative interpretation of the velocity parameter (19). Digital capture and side-by-side comparisons of rest and stress images are standard for both stress echocardiography and radionuclide perfusion imaging, and they should be considered standard for MCE. It is also important to note that because SPECT-sestamibi reflects microvascular blood volume (20), only parametric blood volume maps should be used for comparison. The study also points out some of the limitations of parametric imaging. Fewer segments could be assessed with parametric display than standard gray scale format, and from the illustrative images, basal artifacts are still an obstacle.

**SUMMARY**

At least for the near term, the assessment of myocardial perfusion with non-invasive imaging will be the domain of the clinician and not the computer. The development of automated or semi-automated computerized quantification programs has been driven by the need to enhance the performance of the human interpreter. To this end, the relative impact of new technologies for quantification must be evaluated in terms of whether a technology can improve diagnostic accuracy, standardize interpretation, and derive numerical values that have some clinical consequence.

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**REFERENCES**