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EDITORIAL COMMENT

Is Echocardiography Reliable for Monitoring the Adverse Cardiac Effects of Chemotherapy?*

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Very few would dispute the diagnostic value of echocardiography, which has earned its place in the armamentarium of clinical cardiology by being for decades the only noninvasive imaging modality capable of providing dynamic views of the beating human heart in real time. Most recently, this role has been further enhanced by 3-dimensional (3D) echocardiography, capable of providing unique realistic views of cardiac structures, virtually in real time. It is almost unimaginable today to make a diagnosis of almost any cardiac pathology without ultrasound imaging. Importantly, beyond the visual impact of these images and their contribution to the understanding of normal cardiac function and the recognition of different pathological states, the second most valuable clinical benefit derived from echocardiography is the ability to measure structural and functional parameters, adding another layer to the depth of knowledge of the pathophysiology of disease.

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However, in routine clinical practice this ability cannot be taken for granted, because it inherently depends on the quality of the images used for measurements. Because image quality varies among patients, depending on a variety of well-known factors, the reproducibility of echocardiographic measurements is not uniformly excellent. Consequently, the evaluation of inter-measurement variability of any image-derived parameter has become a standard requirement and an integral part of its validation. Usually, investigators report intra- and inter-observer variability, determined by repeated measurements performed on the same images by observers blinded to the results of prior measurements. Less frequent are reports of the more demanding assessment of test-retest variability, on the basis of repeated image acquisition followed by analysis of different images.

One of the rapidly evolving roles of echocardiography in the management of cancer patients undergoing chemotherapy is the serial evaluation of left ventricular (LV) size and function (1–5). This is precisely the scenario in which test-retest variability, or temporal variability, of the measurement technique is crucial. This is because the premise of serial examinations is that the technique should be sufficiently reliable, such that detection of a critical change over time would indicate a true, clinically meaningful finding rather than reflect random measurement variability.

The study by Thavendiranathan et al. (6) in this issue of the *Journal* focuses on this problem and was specifically designed to identify the optimal echocardiographic technique for the serial evaluation of LV function in cancer patients undergoing chemotherapy, defined by the lowest temporal variability. This study included both 2-dimensional (2D) and 3D echocardiographic measurements, and its results once again demonstrated the advantages of the 3D approach in the context of this critically important clinical problem. Importantly, rather than simply re-imaging and re-measuring LV volume and ejection fraction (EF) to determine the test-retest variability, the investigators made an additional important step by placing their study in the specific context of serial evaluation of these patients over a period of 1 year. To avoid drug-induced changes from being mistaken for temporal variability of the measurements, they appropriately included only patients with stable LV function, as defined by invariably normal global longitudinal strain. This latter parameter of myocardial deformation is increasingly gaining acceptance as a sensitive index of myocardial function on the basis of rapidly growing scientific evidence (7–10).

Although it is widely agreed that in most clinical scenarios inter-measurement variability $<10\%$ of the measured value is acceptable, it is also well-recognized that a measurement technique with such a level of reproducibility is in fact acceptable only if it is aimed at detecting changes that are considerably $>10\%$. If for example the normal value of a normally distributed parameter has an SD that is 2% of the mean, values outside the $\pm 4\%$ range would be considered abnormal. In this case, one should critically assess the value of the measurement technique that has inter-measurement variability as high as 10%, which is considerably greater than the difference that the technique is required to detect. In other words, one cannot rely on a technique with inter-measurement variability that is higher than the difference to be detected.

This limitation of measurement techniques needs to be critically examined, considering that most studies report inter-measurement variability as a mean $\pm$ SD of either the absolute difference between pairs of repeated measurements in percentage of their mean or as the coefficient of variation,

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when more than 2 repeated measurements are performed. This means that measurement variability in individual subjects can be as high as the reported mean measurement variability plus its 2 SD. For example, if a technique was found in a group of 100 patients to have variability of 5 ± 7%, it means that in 10 of the 100 patients the variability was outside the 2-SD range (i.e., the technique could result in differences larger than 5 + 2 × 7%—19% or more), simply because of a random measurement error. Thus, it would be a very legitimate question to ask, "What is the magnitude of change that this technique could detect reliably?" In other words, when a technique is reported to be reproducible within 5%, as determined with repeated measurements, it does not automatically mean that it is capable of reliably detecting differences <5%. Conversely, one should very carefully consider the confidence interval associated with the reported variability.

In the context of the cardiotoxicity of chemotherapy, previous studies have suggested that on consecutive examinations an asymptomatic decrease in LVEF of >10% to <55% or a decrease of >5% to <55%, combined with symptoms of heart failure, might indicate dangerous effects of the drug on the myocardium and should trigger consideration of therapy modification (11). With the aforementioned logic, to be able to detect a 5% change in EF with confidence, the measurement technique should have intermeasurement variability of less than the sum of its reported mean plus its 2 SD at <5%. In other words, the upper limit of the confidence interval needs to be <5% to guarantee that, in 90% of the patients in whom a decrease >5% in LVEF is detected, this decrease would indeed be a meaningful finding and not a measurement error.

To help us interpret their data correctly, Thavendiranathan et al. (6) reported their findings in terms of coefficients of variation with the corresponding confidence intervals. The examination of data in their Online Table A reveals that, among the 6 techniques they tested for the measurement of the 3 parameters (end-systolic and end-diastolic volume and EF), the 3D measurement of EF provided the desired level of reproducibility—as reflected by the upper limit of the confidence interval, which is 4.9% (i.e., just below the 5% target). Importantly, all 4 2D techniques showed temporal variability that was roughly twice as high.

This finding is not surprising in view of multiple recent studies that reported increased accuracy and reproducibility of the volumetric approach compared with the traditional 2D echocardiographic measurements (12). It is widely accepted that this advantage stems from the fact that the 3D measurements are not affected by foreshortened views and do not rely on geometric modeling of the ventricular boundaries. In addition, the software used by Thavendiranathan et al. (6) allows interactive adjustments of the 3D endocardial surface in any arbitrary plane to guarantee for accurate volume calculation.

In summary, this study constitutes an important step toward establishing real-time 3D echocardiography as the imaging modality of choice for the evaluation of the effects of chemotherapy. This is because of its demonstrated capability to detect with confidence changes in LV function that supposedly indicate deleterious effects of chemotherapy (i.e., a drop of >5% in LVEF combined with symptoms of heart failure). It is of note that the findings of Thavendiranathan et al. also (6) indicate that 2D echocardiographic techniques can be reasonably trusted in the detection of a 10% difference in LVEF and used as an indication of cardiotoxicity in the absence of symptoms. This is because the upper limit of the confidence interval of these measurements is roughly 10% (range 9.1 to 11.8). This finding is of particular importance for laboratories that do not yet have access to or the expertise with 3D echocardiography.

Of course, one should remember that these are findings of a single study, albeit with a reasonable sample size. Future studies will show whether the findings reported here can indeed be extrapolated onto the general population of cancer patients undergoing chemotherapy. This question will need to be answered in future multi-center studies. However, the major importance of this study is that it provides the critically needed scientific evidence to support routine clinical use of 3D echocardiography for the monitoring of adverse cardiac effects of chemotherapy. In addition, the evolving use of myocardial deformation indexes might provide additional echocardiographic tools to assess these effects beyond the EF.

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