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EDITORIAL COMMENT

It Is All About Timing!*

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"Observe due measure, for right timing is in all things the most important factor."
—Hesiod, Greek poet, 750 BC to 650 BC (1)

In this issue of *iJACC,* Mada et al. (2) demonstrate the importance of accurate timing in the analysis of global and regional myocardial deformation. The study evaluates different candidate markers of end-diastole and end-systole in a systematic way and includes healthy subjects and patients with myocardial infarction and left bundle-branch block (LBBB). The authors conclude that in hearts with regional pathology, surrogate markers of end-diastole and end-systole are unreliable and should be replaced by mitral and aortic valve closure to avoid clinically relevant errors. As expected, the LBBB group, which was also the group with the lower ejection fraction, was more sensitive to timing errors.

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Method studies are seldom presented at hot-line sessions but are essential for daily clinical practice as well as for scientific progress. At first glance, the study by Mada et al. (2) might not seem that catchy, but the information presented is "hot-line" at the present stage in the development of quantitative deformation imaging. After speckle-tracking echocardiography (STE) was introduced around 2006, it soon knocked out tissue Doppler-based deformation measurements because of less noise and a more intuitive and user-friendly technology. All major vendors developed an STE tool, and the number of publications grew exponentially. At present, we have results showing that global longitudinal strain measured by STE is a measurement with high feasibility that can give incremental diagnostic and prognostic information compared with ejection fraction in a wide range of cardiac diseases (3). So why is global longitudinal strain not a decision tool for left ventricular (LV) function in the guidelines?

This question has recently been addressed by the American and the European imaging societies, and the first part of the answer is, of course, standardization to improve reproducibility across operators, echo labs, and vendors. Studies thus far are mostly single-center, with sparse long-term outcome data. In a joint initiative with the echo vendors, the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) have chosen to focus on global longitudinal strain, and the status of their efforts was recently presented (4). The report by Mada et al. (2) is an important contribution in this process, clearly demonstrating the potential for improved reproducibility if timing is adequately addressed. The second part of the answer is stated in the Echo-roadmap for 2020, published by the ASE; when standardization is satisfactory, deformation imaging can become an integrated part of the routine echo examination (5). This forms the basis for the third and final part of the answer that might open the gates to the guidelines for deformation imaging: large multicenter studies demonstrating impact on long-term outcome.

IS THE ECG OBSOLETE?

Whereas aortic valve closure has already been incorporated as a marker of end-systole in some analysis tools, end-diastole has been defined from the electrocardiograph (ECG). Mada et al. (2) clearly show that this is unreliable, especially in patients with clearly pathological ECGs and mechanical dyssynchrony, e.g., LBBB. The ECG enables us to transfer and compare timing intervals in different recordings within 1 examination and will still be an integrated part of every stored image. However, there is no

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obvious reason for the ASE/EACVI/vendor initiative not to follow the advice given by Mada et al. (2) and to use mitral valve closure as a marker of end-diastole in quantitative deformation measurements. Because the mitral valve is visible in all apical images, an automated solution should be feasible.

2- OR 3-DIMENSIONAL?

Three-dimensional (3D) imaging is here to stay, but the results for regional LV deformation measurements have been disappointing (6). Although anatomic orientation can be improved in 3D, the spatial and temporal resolution is markedly lower than in 2D imaging. Mada et al. (2) do not comment on the implications that their results will have for 3D imaging, but it is evident from their data that a lower temporal resolution increases variation as the result of less accurate timing. Would it be possible for the vendors to transfer some of the technological advances made for 3D imaging back to 2D to improve temporal and spatial resolution and thus tracking quality and accuracy?

REGIONAL DEFORMATION

The data presented by Mada et al. (2) demonstrate that timing is even more important for regional deformation (segmental end-systolic strain). This is expected because regional scar, reduced function, and delayed depolarization lead to both early systolic lengthening and post-systolic shortening. Thus, more rapid changes in segment length take place close to end-diastole and end-systole, rendering the results more susceptible to errors in timing. Although end-systolic strain has been the most widely used variable from deformation analysis, both experimental and clinical studies have shown that peak systolic strain rate carries important pathophysiological information (7,8). Because strain rate is defined as the instantaneous rate of change in length (Eulerian strain rate), the values will not be as dependent on the timing of initial segment length as is strain. However, in STE, peak systolic strain rate is calculated by means of temporal derivation of the strain curve, and low temporal resolution will bias the results.

Timing is not only essential in standardization but is also important in pathophysiological studies. Russell et al. (9) demonstrated this by introducing the concept “wasted myocardial work.” Instead of considering load as an unknown confounder discussed in the “Study Limitations” section, they combined regional deformation measurements with a calibrated LV pressure curve and were able to calculate segmental work during the cardiac cycle. Accurate timing of valve opening and closure was essential for accurate adjustments of the pressure curve. The authors were also able to establish the link between the measured segmental work and myocardial glucose uptake in the same segment during FDG-PET. Adjusting for afterload in this way will decrease variation in strain values caused by differences in load, especially in repeated examinations of the same patient.

The study by Mada et al. (2) illustrates that 1 step back is necessary to be able to go 2 steps forward in the utilization of deformation imaging in clinical practice. The involvement of the vendors is crucial, and sonographers and cardiologists should support the initiative by performing high-quality method studies on specific sources of variation. Furthermore, education is needed to understand the concepts of deformation imaging (10), in which timing of events must be assessed together with the peak values. Standardization is important, but some intellectual input is still necessary to assess measurement quality and sources of error and to combine practical imaging skills and hemodynamic knowledge to understand a clinical problem. The joint ASE/EACVI/vendor initiative should be able to find the right balance between standardization and user-friendliness and the need for sufficient detail and resolution in the measurements.

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