

EDITORIAL COMMENT

The Uncertainties of Certainty

Using LV Function to Predict Arrhythmic Event After AMI*

Zoran B. Popović, MD, PhD

Cleveland, Ohio

A patient comes to your clinic after suffering an anterior myocardial infarction (MI) while sailing off the coast of the Bahamas. Thrombolysis done locally was incomplete, and his ejection fraction (EF), measured by echocardiographic Simpson's biplane method, is 34%. He is now short of breath while walking more than 1 flight of stairs. Given an EF <35%, you recommend implantable cardioverter-defibrillator implantation (1), and explain to the patient the benefits (risk of sudden cardiac death [SCD] decrease) and risks (device infection, inappropriate shocks, tricuspid regurgitation, need for generator change, etc.). Although the patient is willing to proceed with implantable cardioverter-defibrillator placement, he is a statistician by profession. He asks you a question very natural to him. What is the precision of the EF measurement?

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EF assessment by commonly used echocardiography methods is imprecise. Intraobserver standard error of measurement for Simpson's method applied to 2-dimensional echocardiography is 3.3% (2). That means if the same person repeats the measurement of EF after obtaining a value of 34%, the second value (assuming 95% confidence intervals) can be anywhere between 27% and 41%. How can we improve on this uncertainty? One option is to perform a repeat echocardiogram, which increases specificity, but decreases sensitivity. The second option is 3-dimensional echocardiography, which improves the precision of

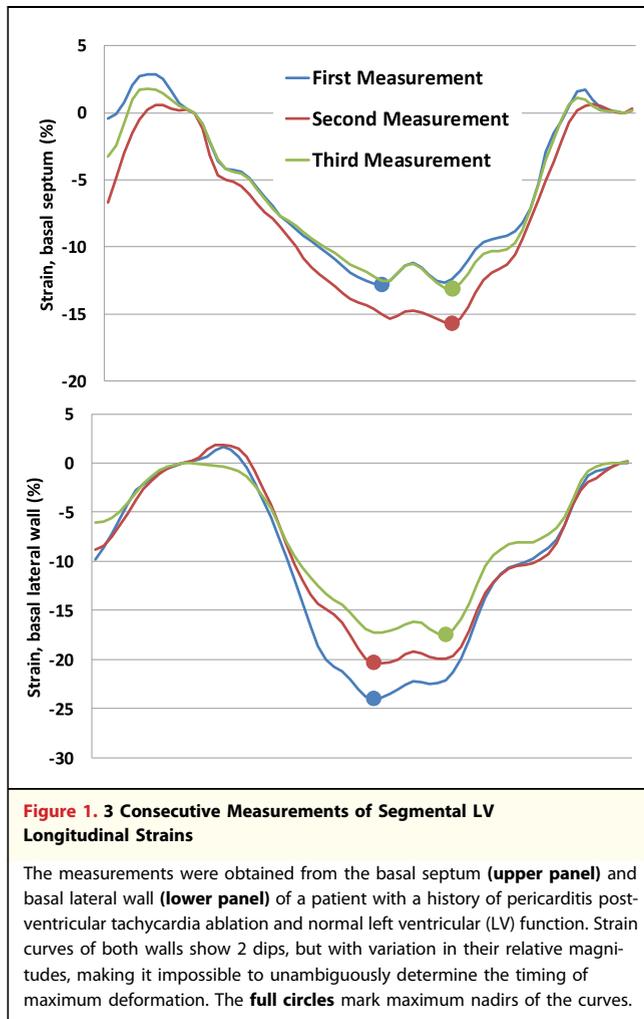
the EF estimation to a better, but still less than ideal, intraobserver standard error of measurement of 1.7% (2). The third option is to use the even more precise, but also more expensive, method of magnetic resonance imaging. Finally, the fourth option is to use another, preferably unrelated, echocardiography measure of left ventricular (LV) dysfunction.

Two papers in this issue of *JACC* evaluate this fourth option (3,4). They address the utility of newer, semiautomatic methods of assessment of long-axis LV function to predict the occurrence of ventricular arrhythmias post-acute MI. The authors use global longitudinal strain (GLS), a marker of long-axis systolic function, and mechanical dispersion (MD), a marker of long-axis "dyssynchrony," to predict the occurrence of arrhythmic events. Both papers show that EF and GLS are lower and MD higher in patients with an arrhythmic event. However, Haugaa et al. (4) found that MD is the only "independent" predictor, whereas Ersbøll et al. (3) found that, according to relative importance, GLS, age, and MD are "independent predictors," with QRS duration and LV volumes having borderline significance.

How congruent are these findings? Should we be measuring long-axis function parameters? How should we incorporate them into day-to-day patient care? The answer to the first question is straightforward—data are very similar. The rule of thumb is that in Cox models, the number of events per predictor variable should be at least 10. In both studies, the number of events was small—15 and 34 events. This means that hazard ratio estimates were wide, and that the number of identifiable "independent" predictors was low—only 1 variable for the first study (3), and only 3 variables for the second (4). Thus, neither of the studies were constructed to evaluate real incremental value of GLS and/or MD once a priori known relevant variables, such as age, sex, QRS duration, and EF were entered into the

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From the Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio. Dr. Popovic has reported that he has no relationships relevant to the contents of this paper to disclose.



model (5). This is especially relevant because GLS shows a strong correlation with EF, which “forces” a stepwise Cox model to choose only 1 of them as predictor even if their comparative predictive values are equal. However, given that these studies are hypothesis generating rather than method validation, they succeed in pointing to MD and GLS as potential predictors of SCD.

Should we add measurements of long-axis function parameters in patients post-MI? Given known uncertainties of EF measurement, well-developed semiautomated methods of GLS assessment, ease of obtaining automated MD, and the fact that the cost of obtaining additional information is zero, the answer is an emphatic yes. In a way, this is equivalent to assessment of hemoglobin, hematocrit, and red blood cell distribution width in a patient with anemia.

The congruence of measurement fortifies decision making, and data discrepancy facilitates identification of borderline patients. Furthermore, use of a new tool can open a window into a reality of which we are not presently aware. This, however, has to be done while using a strict and unambiguous quality control process, given inherent measurement problems. This issue can be illustrated no better than by the right panel of Figure 1 from Haugaa et al. (4), which shows pronounced MD driven largely by a delay of the strain curve of the apical septum (green line). If one inspects this tracing, one sees 2 nadirs of this curve, with a bigger one occurring well after end-systole. The exact mechanism of this type of deformation is hard to ascertain and may be related to both physiological phenomena and methodological artifacts. But what if reanalysis shows the reversal of the relative magnitude of these nadirs? To obtain Figure 1, I performed 3 consecutive segmental strain measurements in the basal septum and lateral walls of a patient with a history of pericarditis post-ventricular tachycardia ablation and normal LV function. There are double nadirs on all of the curves, but with different relative values. With this variability, one can, by chance, get normal, mildly increased, or very pathological MD in a single patient. This strengthens the need for a clear protocol if such analysis is attempted.

Finally, how should we incorporate long-axis function measurement into day-to-day patient care? If the dismal history of echocardiographic “dyssynchrony” parameters as predictors of resynchronization therapy outcomes is our teacher, we should be extremely cautious (6,7). Also, there are only hints, but no unequivocal data, showing that GLS or MD, despite negative clinical markers and normal EF, can predict SCD post-MI. On the other hand, having GLS of -10% (or, for that matter, -14%) is abnormal, no matter what the EF results are. This should prompt either a search for the unrecognized cause of long-axis dysfunction (amyloidosis, hypertrophic cardiomyopathy, etc.) (8) or EF re-evaluation. The important point is to strike a proper balance between the “out with the old, bring on the new” and “everything has been said, and we come too late” (9) world views.

Reprint requests and correspondence: Dr. Zoran B. Popović, Cleveland Clinic, 9500 Euclid Avenue J1-5, Cleveland, Ohio 44195. *E-mail:* popoviz@ccf.org.

REFERENCES

1. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). *J Am Coll Cardiol* 2008;51:e1-62.
2. Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popovic ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. *J Am Coll Cardiol* 2013;61:77-84.
3. Ersbøll M, Valeur N, Andersen MJ, et al. Early echocardiographic deformation analysis for the prediction of sudden cardiac death and life-threatening arrhythmias after myocardial infarction. *J Am Coll Cardiol Img* 2013;6:851-60.
4. Haugaa KH, Grenne BL, Eek CH, et al. Strain echocardiography improves risk prediction of ventricular arrhythmias after myocardial infarction. *J Am Coll Cardiol Img* 2013;6:841-50.
5. Kurl S, Makikallio TH, Rautaharju P, Kiviniemi V, Laukkanen JA. Duration of QRS complex in resting electrocardiogram is a predictor of sudden cardiac death in men. *Circulation* 2012;125:2588-94.
6. Chung ES, Leon AR, Tavazzi L, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 2008;117:2608-16.
7. Beshai JF, Grimm RA, Nagueh SF, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med* 2007;357:2461-71.
8. Phelan D, Collier P, Thavendiranathan P, et al. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. *Heart* 2012;98:1442-8.
9. La Bruyère Jd. Les Caractères de Theophraste traduits du grec; avec les Caractères ou les mœurs de ce siècle [Characters of Theophrastus, Translated From Greek; With the Characters or Manners of This Century]. Paris, France: Estienne Michallet, 1696.

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