In Search of a Holy Grail

Predicting Cardiac Resynchronization Therapy Outcomes by Echocardiography

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“Tt came out of nowhere and captured the cardiology community by storm.” The cliche seems very appropriate when describing the impact of cardiac resynchronization therapy (CRT) on the treatment of heart failure. CRT improves survival rate in symptomatic patients and is the only nonsurgical technique that provides substantial and stable reverse remodeling in both symptomatic and asymptomatic patients. The most surprising fact is that this is accomplished through mechanisms that are still unclear and that are not fully elucidated in experimental models. CRT is the only heart failure therapy with a potential to improve survival rate that is not based on neurohormonal modulation. Finally, it represents a challenge to the imaging community, as it establishes a need to measure something that was previously overlooked—dyssynchrony.

Unfortunately, CRT is not universally successful. One third of CRT patients do not feel better, and close to 40% of patients do not experience reverse remodeling, which is important because it predicts survival rate. This should not be a surprise—treatment of chronic diseases is rarely homogeneously beneficial to all the patients. Nevertheless, in the case of CRT, some extra precautions are necessary. CRT is expensive; placement of electrodes may be difficult; and, even in experienced centers, a significant number of patients may require surgical placement. Finally, it is an expensive, healthcare-intensive therapy with extensive follow-up and occasional complications. Thus, there is an ongoing search for practical methods to predict the outcome of CRT and guide its use. Current guidelines use QRS duration (and symptoms) as the principal determinants for implantation, and as noted, this is fairly successful, with two thirds of such patients demonstrating improvement. The real challenge for clinicians comes in two situations: identifying those patients with narrow QRS who are likely to benefit and identifying those with wide QRS who will not benefit. Mechanical dyssynchrony has been proposed as the key predictor in both of these situations.

The contraction of ventricular segments can be quantified by myocardial velocities, strains, or strain rates. Whereas myocardial velocities simply represent a movement of a segment relative to some reference point, strains measure relative local deformation along 3 major cardiac axes. Plotting the changes of myocardial velocities, strains, or strain rates of individual segments through time can give us insight into ventricular function synchrony. Intraventricular dyssynchrony can then be quantified by how much peak values of these segmental tracings vary in their timing or in their maximal values (amplitudes).

Early on, magnetic resonance imaging strain studies showed that left bundle-branch block leads to uncoordinated contraction of ventricular segments and results in intraventricular mechanical dyssynchrony. Magnetic resonance imaging studies have also shown that earliest contracting segments show mid-systolic blunting of contraction (because of late forceful contraction of lateral segments), often with late-(or even post-) systolic peak. In contrast, late contracting segments contract forcefully because of early stretch and activation of the Starling mechanism. Indeed, this interplay of early and late segments is the basis for using preexcitation of ischemic segments to prevent postinfarct remodeling. Magnetic resonance imaging studies also have shown that CRT decreases both time- and amplitude-based measures of intraventricular dyssynchrony. In addition to this intraventricular dyssynchrony, interventricular dyssynchrony also exists (as is well known to anybody who has auscultated a patient with bundle-branch block), although its importance is less well established.

Analysis of 3-dimensional segmental strains by magnetic resonance imaging is complex and not widely available. Therefore, the echocardiographic community has worked hard to develop predictive methods that are simple, robust, and efficient. Three major questions have emerged from nearly a decade of research: Should one measure dispersion in timings, or in the amplitude, of segmental signals? Should one use velocity- or strain-based measures? Should one measure timing of the onset of contraction or its peak?

The first methods to gain wide acceptance were velocity-based measures of dispersion in timing derived from tissue Doppler imaging. Several single-center studies have shown them to be accurate in predicting the outcome of CRT and to be superior to time-domain strain-based measures of dyssynchrony. Two recent studies that used time-based velocity dyssynchrony measures were not very encouraging, however. The multicenter Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RethinQ) trial did not show that CRT was beneficial to patients with significant...
dyssynchrony but narrow QRS complexes, whereas the large Predictors of Response to CRT (PROSPECT) trial showed that similar velocity-based temporal measures have little prognostic value, challenging their widely believed applicability.

Hence the study of Miyazaki et al and the search for something better. The investigators studied 45 patients before and after biventricular pacing, examining several proposed indices of dyssynchrony. They demonstrated that many of the most popular indices (using time to peak tissue velocity in a variety of segments) did not predict response to resynchronization, whereas time to peak strain showed much better correlation. This was somewhat surprising because several larger previous trials that compared strain and velocity dyssynchrony showed the opposite result. The reasons for this are unclear, though perhaps improvements in both instrumentation and technique (such as narrowing the acquisition sector width) may have allowed strain to overcome its prior problems of excessively noisy signals. On the other hand, failure of velocity data should not be entirely unexpected. Segmental velocities are affected by a number of factors, such as local tethering and apico-basal position. For example, it is fairly common that patients with nonischemic dilated cardiomyopathy and prominent left-to-right rocking motion (longitudinal rotation) have depressed, double-peaked velocities of the basal lateral wall (Figure). This kind of velocity tracing is almost impossible to interpret by standard time-to-peak measures.

So, is this the end of a rainbow? We must recognize several problems with the study by Miyazaki et al. First, it represents a relatively small group of only 45 patients. Given the number of previous studies, some much larger than the present study, one has to be very cautious. Second, the strain measurements were derived from tissue velocity data, which are notoriously noisy and measure only the longitudinal strain component. Indeed, tissue velocity-derived strains may largely be a technique of the past, akin to videocassettes in the era of digital storage. It would have been more meaningful if the authors had used speckle tracking, which appears to present more robust strain data than does tissue velocity imaging. Speckle tracking also provides the potential to obtain not only longitudinal but also circumferential and radial strains that can provide information over and above the ones obtained from longitudinal strain. Also, one must wonder if strain rate, despite its noisy nature, would have provided a useful index, as it would seem to relate more specifically to delays in electrical activation, whereas strain itself has to integrate regional mechanical differences.

An even greater issue to consider is the persistent focus of the echocardiography community on time-based measures of dyssynchrony. Indeed, we have shown in a small study that an amplitude-based measure of dyssynchrony carries some prognostic weight. One could also speculate that methods that incorporate both time and amplitude information would be even more predictive. What is desperately needed, however, are ways to perform and interpret these studies more simply, allowing them to move out of the expert hands.

Figure. Myocardial velocity tracings recorded during 3 cardiac cycles at the base of septal (yellow) and lateral (green) walls in a patient with nonischemic dilated cardiomyopathy and prominent left-to-right rocking motion (longitudinal rotation). Note that lateral wall velocities are blunted, with 2 ejection peaks the relative size of which varies between cardiac cycles (the latter one larger in the first 2 beats, the earlier one in the last beat; see arrows). This type of tracing is difficult to analyze by standard dyssynchrony methods.
of just a few laboratories. One helpful tool would be a
dynamic, bull’s-eye representation of the way strains change
over time to provide an intuitive summary of the timing and
magnitude of contraction. This type of display could help us
define typical patterns of strain development during systole
that underlie patient response to CRT. Ideally, in that situa-
tion, one could determine the necessity of CRT and the ideal
location of the pacing electrode with the same certainty we
have currently in determining the severity and pathoanatomic
location of the mitral valve disease. Until that time, for clinical indications
for CRT, we are left only with the crudest of tools: QRS
complex duration and shape.

Sources of Funding
Dr Thomas is supported in part by the National Space Biomedical
Research Institute through NASA Grant NCC9–58 (Houston, Tex)
and the Department of Defense (Fort Dietrich, Md, USAMRMC
Grant No. 02360007).

Disclosures
None.

References
1. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappen-
berger L, Tavazzi L. The effect of cardiac resynchronization on morbidity
2. Sutton MG, Plappert T, Hilipsch KE, Abraham WT, Hayes DL, Chinchey E.
Sustained reverse left ventricular structural remodeling with cardiac
resynchronization at one year is a function of etiology: quantitative Doppler
ecochardiographic evidence from the Multicenter InSync Ran-
donized Clinical Evaluation (MIRACLE). Circulation. 2006;113:
266–272.
3. Linde C, Gold M, Abraham WT, Daubert JC. Rationale and design of a
randomized controlled trial to assess the safety and efficacy of cardiac
resynchronization therapy in patients with asymptomatic left ventricular
dysfunction with previous symptoms or mild heart failure—the REVerse
Remodeling in Systolic left VEntricular dysfun-
4. Abraham WT, Fisher WG, Smith AL, Delargio DB, Leon AR, Loh E,
Kocovic DZ, Packer M, Clavell AL, Hayes DL, Estelad M, Trupp RJ,
1845–1853.
5. Yu CM, Bleeker GB, Fung JW, Schalij MJ, Zhang Q, van der Wall EE,
Chan YS, Kong SL, Bax JJ. Left ventricular reverse remodeling but not
clinical improvement predicts long-term survival after cardiac resynchron-
Douglas MR, Berger RD, McVeigh ER, Kass DA. Predictors of systolic
augmentation from left ventricular preexcitation in patients with dilated
cardiomyopathy and intraventricular conduction delay. Circulation. 2000;
101:2703–2709.
7. Prinzen FW, Hunter WC, Wyman BT, McVeigh ER. Mapping of regional
myocardial strain and work during ventricular pacing: experimental study
using magnetic resonance imaging tagging. J Am Coll Cardiol. 1999;33:
1735–1742.
8. Vanagt WY, Cornelussen RN, Poulina QP, Blauw E, Vernoo K,
Cleutjens JP, van Bilsen M, Delhaas T, Prinzen FW. Pacing-induced dys-synchrony preconditions rabbit myocardium against ischemia/
9. Wyman BT, Hunter WC, Prinzen FW, Faris OP, McVeigh ER. Effects of
single- and biventricular pacing on temporal and spatial dynamics of
ventricular contraction. Am J Physiol Heart Circ Physiol. 2002;282:
H372–H379.
10. Verbeek XA, Vernoo K, Pescar M, Cornelsn RN, Prinzen FW.
Intra-ventricular resynchronization for optimal left ventricular function
SM, Pires LA, Tchou PJ. Cardiac-resynchronization therapy in heart
failure with narrow QRS complexes. N Engl J Med. 2007;357:
2461–2471.
J, Abraham WT, Ghio S, Leclercq C, Bax JI, Yu CM, Gorcsan J 3rd, St
John Sutton M, De Sutter J, Murillo J. Results of the Predictors of
Response to CRT (PROSPECT) trial. Circulation. 2008;117:
2408–2616.
Karon BL, Rea RF, Hayes DL, Oh JK. Strain dyssynchrony index
correlates with improvement in left ventricular volume after cardiac
resynchronization therapy better than tissue velocity dyssynchrony
MS, Fung JW, Schwartzman D, Chan YS, Tanabe M, Bax JJ. Usefulness
of tissue Doppler velocity and strain dyssynchrony for predicting left
ventricular reverse remodeling response after cardiac resynchronization
15. Yu CM, Zhang Q, Chan YS, Chan CK, Yip GW, Kum LC, Wu EB, Lee
PW, Lam YY, Chan S, Fung JW. Tissue Doppler velocity is superior to
displacement and strain mapping in predicting left ventricular reverse
remodelling response after cardiac resynchronisation therapy. Heart.
2006;92:1452–1456.
16. Popovic ZB, Grimm RA, Ahmad A, Agler D, Favia M, Dan G, Lim P,
Casas F, Greenberg NL, Thomas JD. Longitudinal rotation: an unrec-
gnised motion pattern in patients with dilated cardiomyopathy. Heart.
2009;94:e11.
17. Cho GY, Chan J, Leano R, Strudwick M, Marwick TH. Comparison of
two-dimensional speckle and tissue velocity based strain and validation
with harmonic phase magnetic resonance imaging. Am J Cardiol.
speckle-tracking radial strain from routine black-and-white echocardiog-
graphic images to quantify dyssynchrony and predict response to cardiac
DA. Cardiac dyssynchrony analysis using circumferential versus longi-
tudinal strain: implications for assessing cardiac resynchronization.
20. Popovic ZB, Grimm RA, Perlic G, Chinchoy E, Geraci M, Sun JP,
Donal E, Xu XF, Greenberg NL, Wilkoff BL, Thomas JD. Noninvasive
assessment of cardiac resynchronization therapy for congestive heart
failure using myocardial strain and left ventricular peak power as pa-
rameters of myocardial synchrony and function. J Cardiovasc Elctro-

Key Words: Editorials ■ echocardiography ■ cardiac resynchronization
therapy ■ heart failure ■ pacing ■ pacemakers
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_Circ Cardiovasc Imaging_. 2008;1:3-5
doi: 10.1161/CIRCIMAGING.108.797175

_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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