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Magnetic Resonance Imaging Assessment of Ventricular Dyssynchrony

Current and Emerging Concepts

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Despite the numerous documented benefits of cardiac resynchronization therapy (CRT), a significant proportion of patients undergoing CRT do not demonstrate symptomatic or morphologic improvement, triggering the search to improve targeting of this therapy. Many studies now support direct assessment of mechanical dyssynchrony as a method to better identify CRT responders. Among the methods used, echo-Doppler imaging has taken center stage and is covered in other articles in this special issue; however, these methods have several inherent limitations, and other alternatives are also being explored such as magnetic resonance imaging (MRI). This review discusses the concepts and clinical use of MRI methods for quantitative assessment of mechanical dyssynchrony, highlighting newer acquisition and analysis methods and focusing on how the data can be synthesized into robust indexes of dyssynchronous heart failure. (J Am Coll Cardiol 2005;46:2223–8) © 2005 by the American College of Cardiology Foundation

Despite the well-documented beneficial effects and overall efficacy of cardiac resynchronization therapy (CRT) (1,2), approximately 20% to 30% of patients receiving CRT do not demonstrate symptomatic improvement (3). A primary concern is that electrical surrogate measurements for chamber dyssynchrony, such as QRS duration, inadequately identify mechanical dyssynchrony (4) and weakly predict both the acute and chronic CRT response (5,6). An alternative to the QRS complex is to examine mechanical dyssynchrony by the analysis of wall motion, and recent studies have shown this to be a better predictor of both acute and chronic improvement from CRT (7,8). Most mechanical dyssynchrony analysis is based on echo-Doppler methods, which in turn are largely derived from only two-dimensional longitudinal motion data. This choice of orientation is mainly based on practical grounds given available windows for transducer placement. However, cardiac contraction is principally circumferential, and thus echo-based Doppler methods may not provide the most accurate and comprehensive assessment of global dyssynchrony in heart failure. Further, the variance of repeated B-mode and Doppler two-dimensional echocardiographic measures is fairly high owing to dependence on operator experience, machine settings, available acoustic windows, and angle of incidence effects. This can introduce noise when applying such approaches to the routine clinical setting.

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Quantitative magnetic resonance imaging (MRI)-based strain analysis provides highly reproducible, high-resolution three-dimensional circumferential and longitudinal myocardial activation data that are largely operator- and patient-independent and thus may be better suited to characterize dyssynchronous heart failure and identify appropriate candidates for CRT. Although this approach has been traditionally considered for research use only and incompatible with implanted devices, this status is changing rapidly, which may have important implications for the use of MRI as a standard method to assess CRT candidates and define a "response" to CRT.

In this review, we focus on the rationale and technical basis for the use of MRI methods for assessment of dyssynchrony. Specifically, we highlight existing and emerging MRI acquisition and analysis methods for myocardial dyssynchrony analysis and present the various methods for synthesizing and converting their complex data output into simple and sensitive indexes for dyssynchrony assessment. Lastly, we will briefly update the status of CRT device MRI compatibility and its implications for accurate dyssynchrony assessment in patients after CRT implantation.

MRI STRAIN ACQUISITION METHODS FOR DYSSYNCHRONY ASSESSMENT

Cine mode MRI is an excellent imaging modality for the assessment of global and regional myocardial function in patients with contractile dysfunction (9). This method captures multiple slices and phases of the heart to generate what appears to be a real-time representation of cardiac contraction. Global function is measured by simple volumetric analysis of the left ventricle, whereas regional myocardial function is most commonly derived from qualitative

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Abbreviations and Acronyms

CRT = cardiac resynchronization therapy
HARP = harmonic phase
MRI = magnetic resonance imaging
SENC = strain-encoded

wall motion assessment and/or quantitative methods that track myocardial deformation over the cardiac cycle. Although several studies have applied MRI-based quantitative regional function to assess myocardial dysfunction in patients with ischemic and non-ischemic heart failure, the application of cine-MRI specifically to aid CRT-related issues (e.g., optimal patient selection, pacing protocol optimization) is relatively underdeveloped. The evolution of advanced MRI quantitative strain pulse sequence algorithms designed to work with traditional cine-MRI, as well as new methods to analyze their output, have opened new avenues for assessment of cardiac dysfunction. We next review the status of these existing and emerging MRI acquisition and analysis methods for characterizing dyssynchronous heart failure and their applicability for dyssynchrony assessment.

Cine myocardial tagging. Magnetic resonance imaging myocardial tagging is a technique that places non-physical markers (stripes or grids) inside the myocardium by manipulating the magnetization of the tissue using special encoding pulses (10,11). These markers, called tags, appear in the acquired images as dark lines and serve as fiducial myocardial markers that move and bend with the myocardium to which they are linked (Fig. 1A). In addition to simplifying the visual/qualitative assessment of cardiac wall motion abnormalities, analysis of the relative movement of these tags over the cardiac cycle is used to calculate local myocardial motion or strain. Strain can be defined as change in the length per unit length—much like relative shortening. There are three primary strains for three-dimensional deformation—circumferential, radial, and longitudinal (Fig. 1B)—and each can be computed. Techniques for such

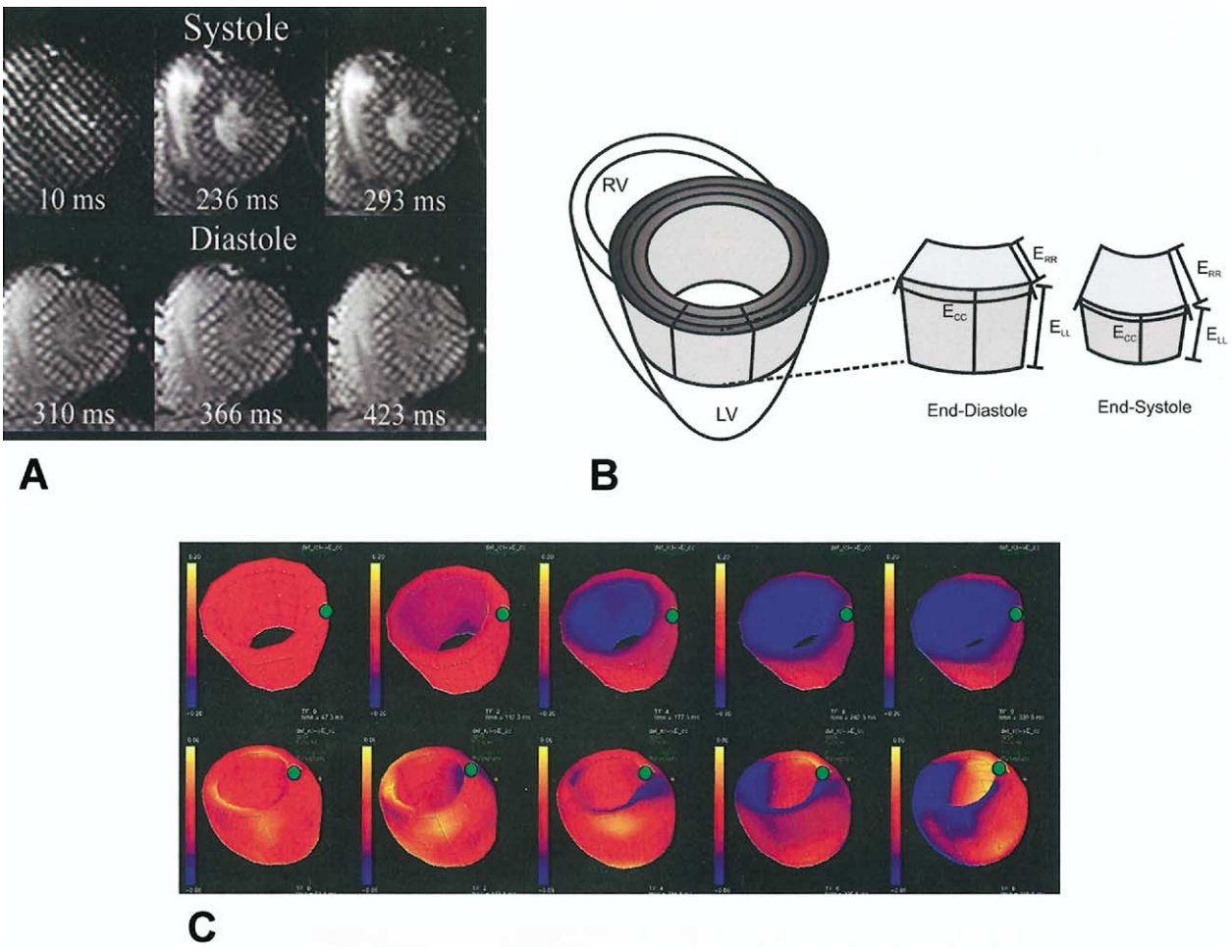

Figure 1. **(A)** Temporal series of images demonstrating magnetic resonance imaging myocardial tagging during systole **(upper panels)** and diastole **(lower panels)** and **(B)** an illustration showing the direction of myocardial strains. **(C)** Individual phases from the cardiac cycle showing the spatial and temporal evolution of three-dimensional circumferential strain for a normal healthy human heart **(upper panels)** and a patient with severe cardiomyopathy and left bundle branch-type conduction delay **(lower panels).** Time moves from left (end-diastole) to right (end-systole). During systolic contraction, the spatial and temporal distribution of circumferential strain are visualized by the color changes, where **red** corresponds to the neutral (end-diastolic) strain, **blue** is shortening, and **yellow** is lengthening or stretch. E_{CC} = circumferential strain; E_{LL} = longitudinal strain; E_{RR} = radial strain; LV = left ventricle; RV = right ventricle.

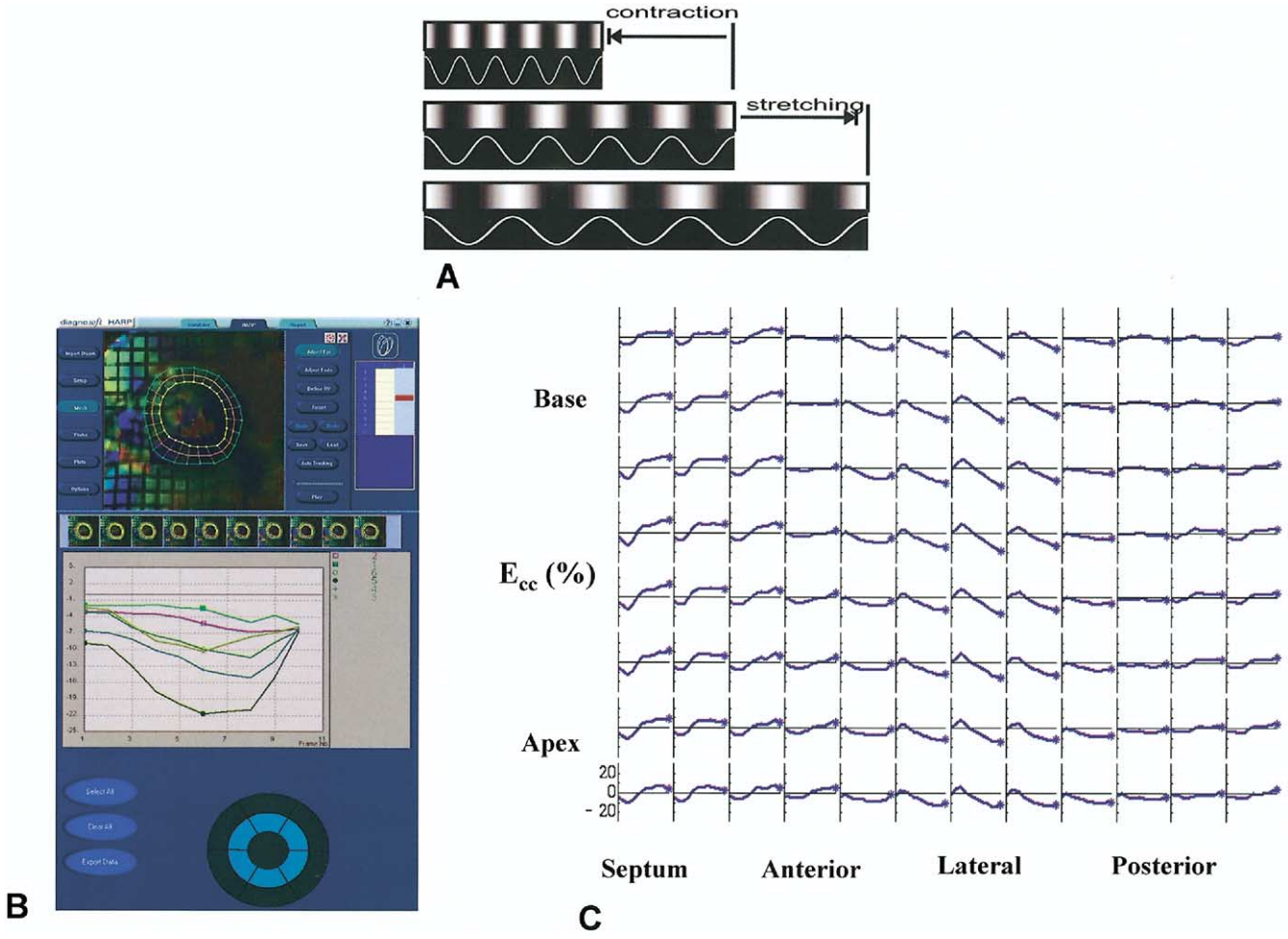

Figure 2. **(A)** Illustration showing the relationship between local strain and tag frequency for harmonic phase-based strain measurements. The contraction of a tagged fiber in the middle would increase the tagging frequency (density of tag lines) as shown in the top fiber. Stretching causes a reduction in local frequency. **(B)** Two-dimensional segmentation of the heart and mesh generation **(top panel)** and regional strain versus time plots over the cardiac cycle; **(C)** complete regional strain versus time plots over the cardiac cycle for all segments. E_{CC} = circumferential strain.

analysis were developed by O'Dell et al. (12) to generate detailed four-dimensional mechano-anatomic activation maps from MRI tagged data sets (Fig. 1C). The analytic algorithm (FINTAGS) has been used to characterize mechanical dyssynchrony in animal models (13,14) and in humans with heart failure and intraventricular conduction delay (15,16) (see Fig. 1C caption for details). Although the information generated by this approach is comprehensive, processing and analysis time is extensive, limiting its clinical utility.

Harmonic phase analysis of tagged MRI. To enhance the clinical utility of myocardial tagging data acquisitions, a rapid analysis method called harmonic phase (HARP) has recently been developed (17) and commercialized (Diagnosoft, Inc., Palo Alto, California). This approach shortens the analysis time to generate regional dynamic color stain maps/data from 1 week to under 2 min for three to four myocardial slices. The HARP method measures the motion from tagged magnetic resonance images by filtering certain regions in the frequency domain of the images called harmonic peaks (18,19). The resulting image is then decomposed into a harmonic magnitude and harmonic phase, which are related to the underlying anatomy of the heart and tag deformation, respectively. The HARP method measures the local strain of tissue by measuring the frequency of the tag lines. This can be best understood by considering a segment of myocardial tissue with a tagging pattern as shown in Figure 2A. The number of tags per unit length is called the frequency of the tag pattern. If this tissue contracts, the tag lines become closer to each other and the tag frequency increases in proportion to that contraction, and vice versa. Circumferential strain in a given angular sector of each slice is then plotted during the cardiac cycle (Figs 2B and 2C).

The HARP technique has been validated and used in several studies to quantitatively characterize region function in animals and patients with myocardial infarction (20). Recently, our laboratory used a two-dimensional HARP analysis for characterization of the optimal left ventricular pacing site for bi-pacing in a canine model of dyssynchro-

nous heart failure (21) as well as in patients with ischemic dyssynchronous heart failure to isolate the effect of infarct extent and location (22).

Strain-encoded MRI. Although faster, HARP analysis still requires some post-processing. A more automatic alternative is strain-encoded (SENC) MRI, a new method for direct imaging of regional strain that does not require complex image processing (23). The SENC imaging is derived from a standard myocardial tagging sequence that tags the tissue at end-diastole with a sinusoidal tag pattern designed to modulate the longitudinal magnetization orthogonal to the imaging plane. Deformations of tissue during systole will change the local frequency of the pattern in proportion to the through-plane strain component. The distribution of regional contraction (circumferential shortening in long-axis views or longitudinal compression in short-axis views) is then displayed as contrast in the images (Fig. 3, see caption for details). The SENC technique has several features that make it especially well suited for assessing dyssynchronous heart failure and CRT, in that it provides: 1) instantaneous real-time quantitative strain measurements without the need for user intervention; 2) higher spatial resolution over standard tagging as a result of reduced tag spacing; 3) allows acquisition of both circumferential and longitudinal myocardial stain information; and 4) application to assessment of regional function of the right as well as the left ventricle.

Recent software tools to reconstruct and quantify SENC images allow real-time calculation and display of changes in regional circumferential shortening and longitudinal compression throughout the cardiac cycle. Ongoing work at our institution is applying this method to cardiac CRT evaluation in both animals and patients.

MRI STRAIN DERIVED DYSSYNCHRONY INDEXES

Once the time-varying image of wall motion and measures of regional contraction amplitude or phase using the MRI methods described in the previous sections have been extracted, the question then becomes how to synthesize this rich and complex data set into a simple, sensitive, and specific measure of cardiac dyssynchrony. The design and construction of the ultimate dyssynchrony index requires not only the raw metric ingredients of strain, position, and time, but also a thorough understanding of the underlying physiology of dyssynchronous heart failure to help guide the appropriate mathematical synthesis of these metrics. In the following sections, we present various MRI strain- and phase-based dyssynchrony indexes that we currently implement at our institution in both clinical and animal studies.

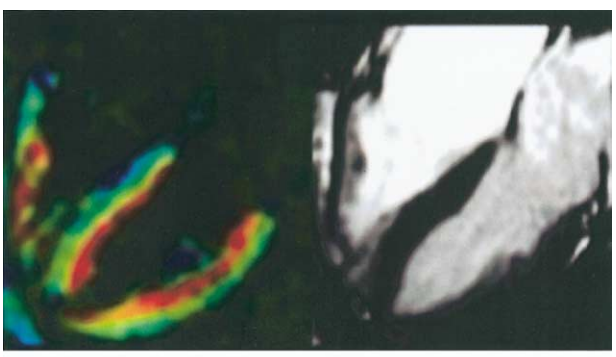

Figure 3. Comparison of a strain-encoded circumferential strain image **(A)** and the corresponding phase matched steady-state free precession sequence in a normal healthy volunteer **(B)**. Note the uniform transmural strain gradient at the septum and left ventricular lateral wall.

Regional variance of strain. The regional variance of strain is determined from the variance of strain magnitude obtained from 28 radially displaced segments for each short-axis section and averaged among slices for each time point. This approach is most similar to many commonly used indexes based on tissue Doppler functional imaging (7). An alternative has been to simply count the total number of regional segments with delayed shortening (expressed as a percent of total regions examined) (16). There are, however, problems with these approaches, as shown in Figure 4A. In one example, segments with delayed contraction are clustered along one portion of the left ventricular wall (upper panel), whereas in the other they are dispersed throughout the heart more homogeneously (lower panel). If the times of primary contraction for each radial site are measured and variance (or total number of delayed segments) determined, the result is identical for both examples. Indeed, electrical activation would also be delayed and QRS duration longer in both. Yet the impact on mechanical dyssynchrony will be markedly different, with only the heart in which segments are clustered having discoordinate contraction.

Regional variance vector of principal strain. An alternative approach to regional variance of strain is regional variance vector of principal strain, where a unit vector points to each region and is then multiplied by a scalar, which can be the time at maximal shortening (strain) or instantaneous magnitude of that strain. The vector sum will only have a significant magnitude if delayed versus early regions are geographically clustered (Fig. 4A, lower panel). This type of analysis was first applied to MRI-based imaging by Wyman et al. (24), and recently by Helm et al. (25), but can be easily used with any image in which multiple regions are assayed.

Temporal uniformity of strain. Yet another method to index three-dimensional dyssynchronous contraction is called temporal uniformity of strain (14,25). In this method, time plots of strain (shortening/stretching) are generated at each of 28 evenly distributed segments around a short-axis slice (Fig. 4B). Each dynamic strain versus myocardial location plot is then subjected to Fourier analysis and decomposed into zero and first-order terms. If all segments shorten simultaneously (perfectly synchronous contraction), the plot appears as a straight line, whereas regionally clustered dyssynchrony (i.e., territory of early vs. late activation) generates an undulating plot with higher power in the first-order term. Shown in Figure 4C are two examples

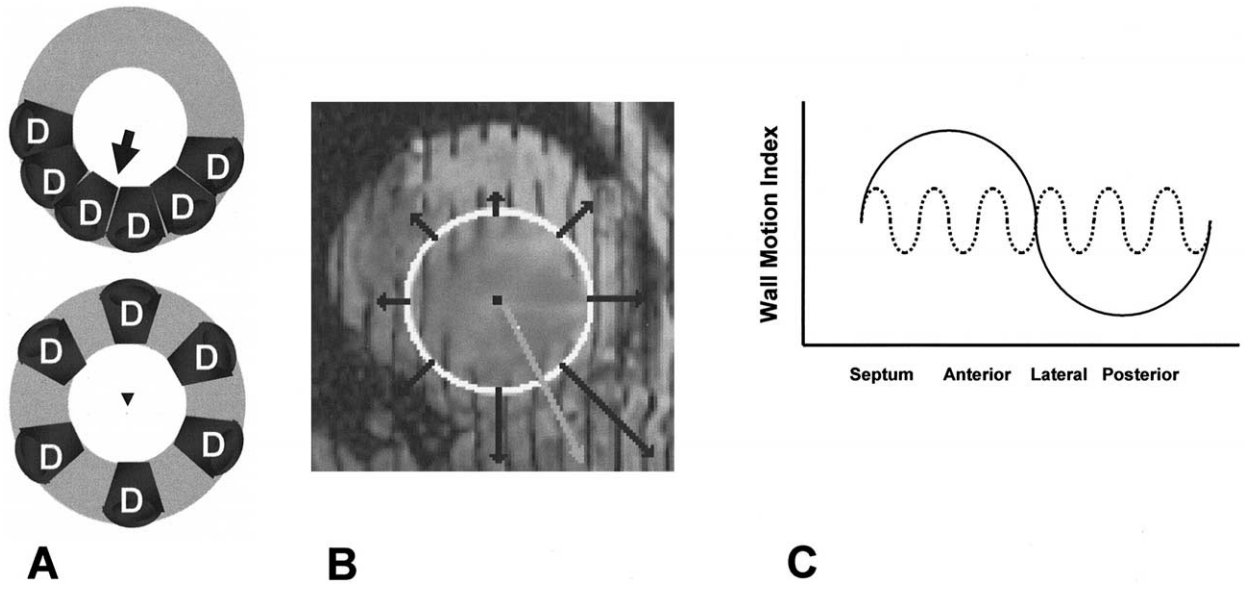

Figure 4. **(A)** Schematic model of hearts with delayed segments clustered in one region versus spaced about the myocardium. Depending on how one indexes dyssynchrony, the result could be the same for both situations, despite markedly different impacts on dyssynchrony. **(B)** Calculation of a vector-dyssynchrony index. Values of regional shortening (strain) or time of peak shortening are determined at various positions in the cross section. These are then multiplied by a unit vector pointing in that direction, and the vectors are summed to generate the net **(gray)** vector magnitude. Greater net vector magnitude reflects dyssynchrony. **(C)** Determination of the temporal uniformity of strain or circumferential uniformity ratio estimate index. A measure of wall motion or timing value is plotted versus location. Overall dyssynchrony appears as a sine-wave (analogous to the situation shown at **top panel of A**). If delays are dispersed through the wall **(lower panel of A)**, the plot appears as the **dotted line**. By determining the low-frequency content of these plots, one derives the dyssynchrony index.

corresponding to the hearts in Figure 4A. The heart with clustered regions shows delays in one territory versus the other so this plot appears more or less sinusoidal. The other heart shows more variability around the heart, yielding a higher frequency waveform. If one applies a low-pass filter (i.e., relative amplitude of the first harmonic normalized to the mean), then only the former will indicate dyssynchrony; the latter will not. This approach was used by Leclercq et al. (14) and referred to as the circumferential uniformity ratio estimate; it was recently described in more detail by Helm et al. (25) who also reported that temporal uniformity of strain/circumferential uniformity ratio estimate compares favorably with vector sum methods.

CRT AND MRI DEVICE COMPATIBILITY

Although new methods have substantially improved the practicality of MRI CRT assessment, there remain a number of concerns, including cost, longer examination times, need for complex imaging/data processing infrastructure, and, perhaps most importantly, inability to image patients with implanted devices. As discussed, the examination time and analysis do not need to be cumbersome, and clinical costs have been reduced to compare favorably with comprehensive echo-Doppler studies. Regarding the issue of imaging patients with implanted devices, our laboratory and others have recently found that this traditional taboo is no longer valid. Such studies have shown that animals with chronically implanted devices can undergo cardiac myocardial MRI tagging using clinically relevant gradient echo sequences without evidence of device malfunction, unintentional lead heating, or prohibitive lead artifacts (26). This report also included data from 21 patients with implanted devices undergoing clinically indicated MRI scans (e.g., musculoskeletal, neurologic, and cardiac), again finding no complications or indications of device malfunction. Since then, we have gained experience performing MRI tagging studies in patients with CRT devices and have been able to successfully acquire high-quality MRI tagged images (Fig. 5) that can be used for accurate quantitative analysis (Lardo et al., unpublished data, 2005). Such positive findings are likely due to both improved MRI-compatible materials used

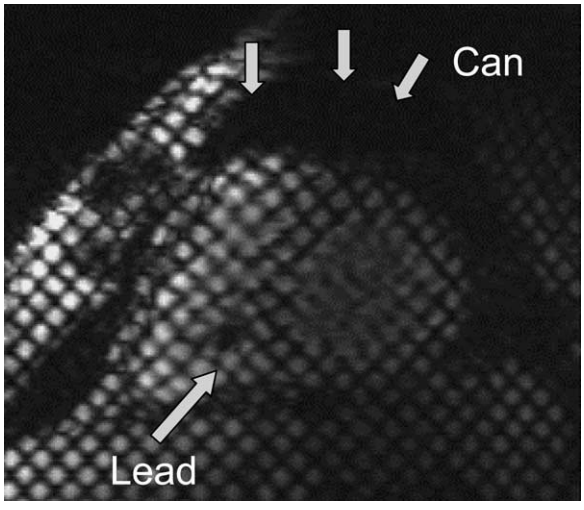

Figure 5. Representative images illustrating lead artifacts seen in magnetic resonance images.

in device construction and advanced electronic filtering that improves immunity to electromagnetic inference. These advances, combined with better understanding of the basic physics of device and MRI pulse sequence interactions from extensive phantom and animal testing, have recently all but shattered the traditional device contraindication for MRI. This change has clear implications for MRI-based dyssynchrony and CRT assessment as the clinical utility of MRI may now be expanded from pre-device implantation studies for identification of appropriate candidates to serial global and regional characterization of the chronic response to CRT (e.g., reverse remodeling). This represents a truly exciting potential advance that may ultimately allow the development of a three-dimensional clinical gold standard for assessing CRT benefits.

SUMMARY

The MRI-based assessment of mechanical dyssynchrony is feasible and provides reproducible three-dimensional circumferential and longitudinal and activation information. Advances in the rapid analysis of tagged magnetic resonance images such as HARP and SENC and the design of novel global indexes of cardiac dyssynchrony may provide a more comprehensive method for selecting ideal candidates for CRT and help facilitate the design of optimal pacing algorithms. Lastly, the future ability to perform MRI dyssynchrony assessment both before and after implantation in the same patient population may allow for clear and standardized definitions for "responders" to CRT.

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REFERENCES

1. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873–80.
2. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–53.
3. Kass DA. Ventricular resynchronization: pathophysiology and identification of responders. Rev Card Med 2003;4:S3–13.
4. Bleeker GB, Schalij MJ, Molhoek SG, et al. Relationship between QRS duration and left ventricular dyssynchrony in patients with end-stage heart failure. J Cardiovasc Electrophysiol 2004;15:544–9.
5. Pitzalis MV, Iacoviello M, Romito R, et al. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. J Am Coll Cardiol 2002;40:1615–22.
6. Bax JJ, Ansalone G, Breithardt OA, et al. Echocardiographic evaluation of cardiac resynchronization therapy: ready for routine clinical use? A critical appraisal. J Am Coll Cardiol 2004;44:1–9.
7. Yu CM, Chau E, Sanderson JE, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002;105:438–45.
8. Bax JJ, Molhoek SG, van Erven L, et al. Usefulness of myocardial tissue Doppler echocardiography to evaluate left ventricular dyssynchrony before and after biventricular pacing in patients with idiopathic dilated cardiomyopathy. Am J Cardiol 2003;91:94–7.
9. Bogaert JG, Bosmans HT, Rademakers FE, et al. Left ventricular quantification with breath-hold MR imaging: comparison with echocardiography. Magma 1995;3:5–12.
10. Axel L, Dougherty L. MR imaging of motion with spatial modulation of magnetization. Radiology 1989;171:841–5.
11. Zerhouni EA, Parish DM, Rogers WJ, Yang A, Shapiro EP. Human heart: tagging with MR imaging—a method for noninvasive assessment of myocardial motion. Radiology 1988;169:59–63.
12. O'Dell WG, Moore CC, Hunter WC, Zerhouni EA, McVeigh ER. Three-dimensional myocardial deformations: calculation with displacement field fitting to tagged MR images. Radiology 1995;195:829–35.
13. 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;33:1735–42.
14. Leclercq C, Faris O, Tunin R, et al. Systolic improvement and mechanical resynchronization does not require electrical synchrony in the dilated failing heart with left bundle-branch block. Circulation 2002;106:1760–3.
15. Curry CW, Nelson GS, Wyman BT, et al. Mechanical dyssynchrony in dilated cardiomyopathy with intraventricular conduction delay as depicted by 3D tagged magnetic resonance imaging. Circulation 2000;101:E2.
16. Nelson GS, Curry CW, Wyman BT, et al. Predictors of systolic augmentation from left ventricular preexcitation in patients with dilated cardiomyopathy and intraventricular conduction delay. Circulation 2000;101:2703–9.
17. Osman NF, Kerwin WS, McVeigh ER, Prince JL. Cardiac motion tracking using CINE harmonic phase (HARP) magnetic resonance imaging. Magn Reson Med 1999;42:1048–60.
18. Osman NF, Prince JL. Visualizing myocardial function using HARP MRI. Phys Med Biol 2000;45:1665–82.
19. Osman NF, McVeigh ER, Prince JL. Imaging heart motion using harmonic phase MRI. IEEE Trans Med Imaging 2000;19:186–202.
20. Kraitchman DL, Sampath S, Castillo E, et al. Quantitative ischemia detection during cardiac magnetic resonance stress testing by use of FastHARP. Circulation 2003;107:2025–30.
21. Helm R, Byrne M, Daya S, et al. Characterization of the optimal left ventricular pacing region in dyssynchronous heart failure: implications for biventricular cardiac resynchronization (abstr). Heart Rhythm 2005;2 Suppl:S8.
22. Helm RA, Wu K, Fernandes V, et al. Quantitative MRI assessment of cardiac dyssynchrony in patients with ischemic cardiomyopathy: effect of infarct location. Circulation 2005. In press.
23. Osman NF, Sampath S, Atalar E, Prince JL. Imaging longitudinal cardiac strain on short-axis images using strain-encoded MRI. Magn Reson Med 2001;46:324–34.
24. 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:H372–9.
25. Helm RH, Leclercq C, Faris OP, et al. Circumferential versus longitudinal motion-based analysis of cardiac dyssynchrony implications for assessing cardiac resynchronization. Circulation 2005;111:2760–7.
26. Roguin A, Zviman MM, Meininger GR, et al. Modern pacemaker and implantable cardioverter/defibrillator systems can be magnetic resonance imaging safe: in vitro and in vivo assessment of safety and function at 1.5 T. Circulation 2004;110:475–82.