Cardiac Diffusion Tensor MRI

Daniel B. Ennis[1,2,3]; Eric Aliotta[1,2]; Holden H. Wu[1,2,3]

[1] Department of Radiological Sciences, University of California, Los Angeles, CA, USA
[2] Biomedical Physics Interdepartmental Program, University of California, Los Angeles, CA, USA
[3] Department of Bioengineering, University of California, Los Angeles, CA, USA

Introduction

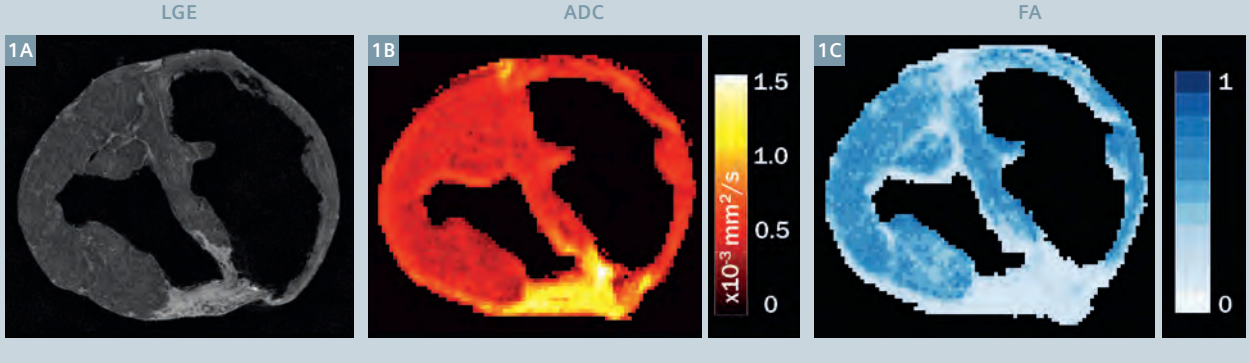
Cardiac motion occurs at many scales. Fast and slow. Big and small. MRI has developed over several decades to freeze the motion of the heart or capture its dynamics all of which has led to advanced diagnostic methods for evaluating heart function. Central to our ability to freeze cardiac motion has been increasingly advanced gradient hardware [1]. Initially, this permitted capturing the dynamics of the beating heart in a breath-hold [2]. More recently, the fast and ultrafast gradient hardware permits encoding the diffusive motion of water molecules in a beating heart!

What can we measure?
Imaging the self-diffusion of water in the beating heart – termed cardiac diffusion weighted imaging (cDWI)[1] – presents numerous challenges, but also makes available new mechanisms for generating image contrast. cDWI is poised to provide molecular-level, quantitative insight to microstructural organization and changes in organization (i.e. remodeling) that occur with disease. For example, sensitivity to changes in the apparent diffusion coefficient (ADC, mm^2/s) provides information about how freely water molecules diffuse. Another measure, termed fraction anisotropy (FA), characterizes the directional dependence of the diffusion and is zero for tissues that have isotropic microstructure and can be as high as one for highly anisotropic tissues [3].

[1] The product is still under development and not commercially available yet. Its future availability cannot be ensured.

How do cDWI parameters change?
Much of what we know about *in vivo* changes in ADC comes from the neuro literature wherein it is widely appreciated that ADC decreases in acute strokes, pseudo-normalizes within weeks, and subsequently increases above baseline [4]. Currently, less is known about *in vivo* changes to ADC in areas of acute myocardial infarction, but similar findings have been reported [5]. ADC is known to increase significantly in diffuse fibrosis [6] and more so in chronic infarcts [7]. In fact, because *ex vivo* cardiac DT-MRI has been practical already for several years we can easily observe the diffusive-level changes in chronic infarcts. Our detailed *ex vivo* work in chronic swine infarcts clearly demonstrates that the ADC is significantly elevated and that the FA is significantly decreased within the infarct, both of which show excellent correlation to the region identified using post-contrast T1-weighted MRI (Fig. 1). As *in vivo* cardiac diffusion weighted imaging becomes more widely available these findings are sure to be reported.

cDWI for myocardial infarcts?
Myocardial infarctions (MI) are the most common form of heart disease and a leading cause of death worldwide [8]. Non-invasive imaging methods for identifying and characterizing affected regions are critical to the diagnosis of MI and the management of post-MI ventricular remodeling [9, 10]. LGE MRI has demonstrated significant clinical value as the gold standard in detecting the location and extent of MI [11]. However, the injection of a GBCA is contraindicated in



1 T1-weighted LGE MRI **(1A)**, apparent diffusion coefficient (ADC) **(1B)** and fractional anisotropy (FA) **(1C)** in an infarcted porcine heart *ex vivo*. Regions of increased ADC and decreased FA match similar regions of hyper-intense signals in the corresponding LGE MRI slice.

patients with poor renal function, which poses a significant limitation because this group comprises ~40% of patients with cardiovascular disease and also exhibits increased cardiovascular mortality rates [12]. There does not currently exist a clinically acceptable imaging method for detecting and evaluating MI in this large and high-risk patient group. cDWI may be able to fill this role.

How is the heart microstructurally organized?

The heart is comprised of billions of individual myocytes coordinated into a highly organized network best described as a continuously branching syncytium. In the healthy heart, the organized myocytes are grossly characterized by a transmural change in orientation. The myocytes are further organized into bundles termed sheetlets [13] whose dynamics give rise to ventricular wall thickening [14]. Shortening along the myocyte's long-axis and shearing between the sheetlets are both critical to ventricular performance.

How does cDWI estimate directional information?

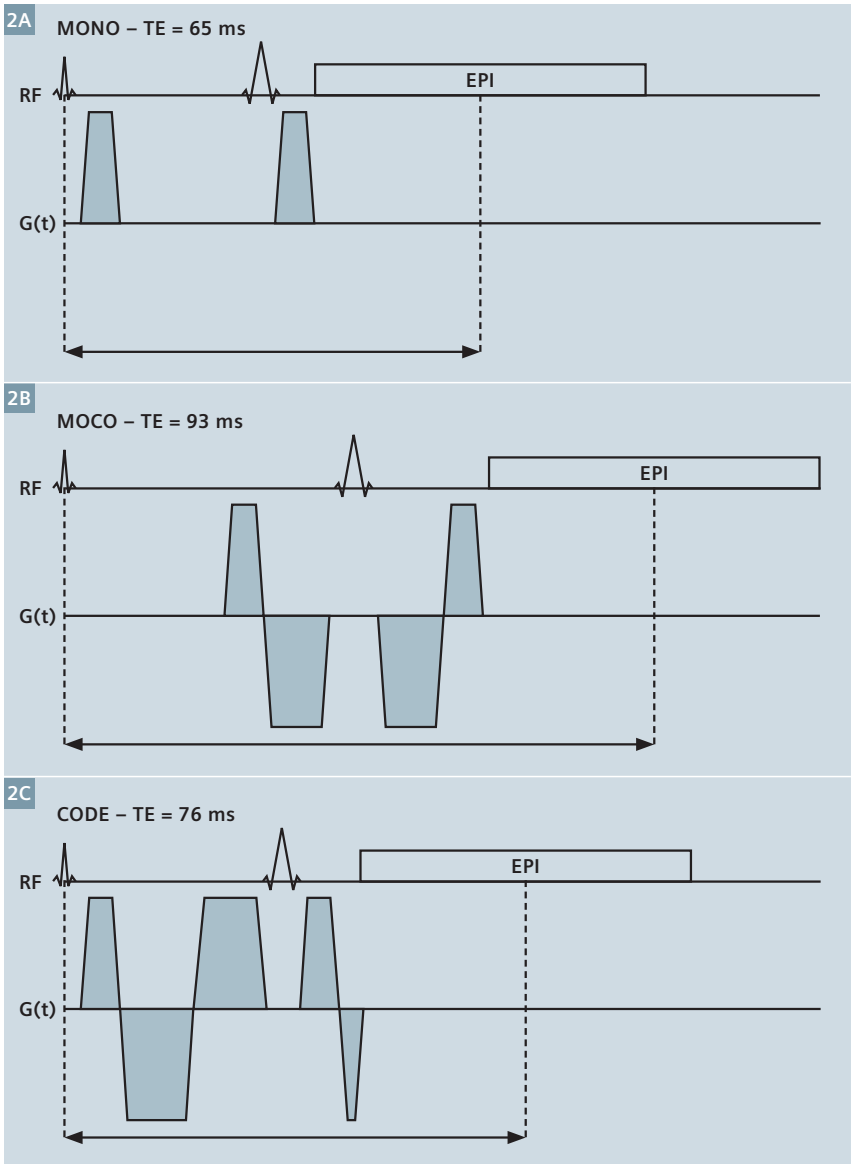
cDWI can be used to estimate the local diffusion tensor which comprises information about the magnitudes of diffusion (e.g. ADC and FA) and also the directionality of diffusion. We know from careful *ex vivo* work that the primary eigenvector of the diffusion tensor corresponds to the long axis of the myocytes [15] and that the tertiary eigenvector is generally related to the surface normal of the local sheetlets [16]. Consequently, *in vivo* measurement of the diffusion tensor provides direct insight to changes in microstructural orientations in health and disease [17].

What about the bulk motion sensitivity of DWI?

cDWI measures diffusive motion on the microscopic scale using diffusion encoding gradients with large amplitudes (40 to 80 mT/m) and significant durations (5-10 ms is typical). Consequently, even subtle cardiac bulk motion can significantly corrupt the cDWI measurements unless steps are taken to carefully mitigate bulk motion artifacts. Several approaches have been proposed to address this issue. For example, diffusion encoding with STimulated Echo Acquisition Mode (STEAM) [18] limits bulk-motion sensitivity by using very short diffusion encoding gradients distributed across two heartbeats. This approach has been widely adopted and is quite promising, but necessarily has a longer scan time due to two heartbeat encoding, modest SNR because of the stimulated echo, and is confounded by cardiac strain sensitivity and heart rate variability [19].

cDWI with SE-EPI as an alternative to STEAM?

An alternative is single-shot spin-echo (SE) echo planar imaging (SE-EPI) which is insensitive to strain and has better SNR performance and shorter scan times than STEAM [20]. However, SE-EPI cDWI with traditional monopolar encoding is highly sensitive to cardiac bulk motion and requires customized acquisition strategies and post



2 cDWI pulse sequence diagrams for **(2A)** bulk-motion sensitive, monopolar (MONO) encoding; **(2B)** non-optimized motion compensated (MOCO) encoding and **(2C)** Convex Optimized Diffusion Encoding encoding with M_1 and M_2 motion compensation (CODE) (b = 350 s/mm² and 1.5 x 1.5 mm in-plane resolution) which eliminates sequence dead time and reduces TE compared to MOCO.

processing to achieve acceptable image quality [21].

How can bulk motion sensitivity be mitigated?

One approach to mitigating bulk motion artifacts is to use diffusion encoding gradient waveforms that are insensitive to bulk motion, but still sensitive to diffusive motion. Recent work has shown that motion compensated (MOCO) diffusion gradient waveforms with nulled first (M_1) and second (M_2) moments (time-weighted gradient waveform integrals) that are unaffected by bulk linear velocities and accelerations, can also encode diffusion in the presence of cardiac motion [22-24]. When applied to SE-EPI cDWI, MOCO gradients combine bulk motion robustness with strain insensitivity and short scan times. However, moment nulling for the diffusion encoding gradients (i.e. MOCO) necessarily increases the total diffusion encoding duration as compared to monopolar waveforms (Fig. 2). Consequently, conferring bulk motion insensitivity unavoidably increases the echo time (TE), which reduces SNR. This is exacerbated in high-resolution imaging with long EPI readout intervals, which introduces lengthy dead times within the sequence before the refocusing pulse (Fig. 2). This generally limits cDWI to ~2.5 mm in-plane resolution, which is insufficient for evaluation of myocardial infarcts per cardiac MRI guidelines [25]. Herein we describe a technique that we have found to largely overcome this limitation.

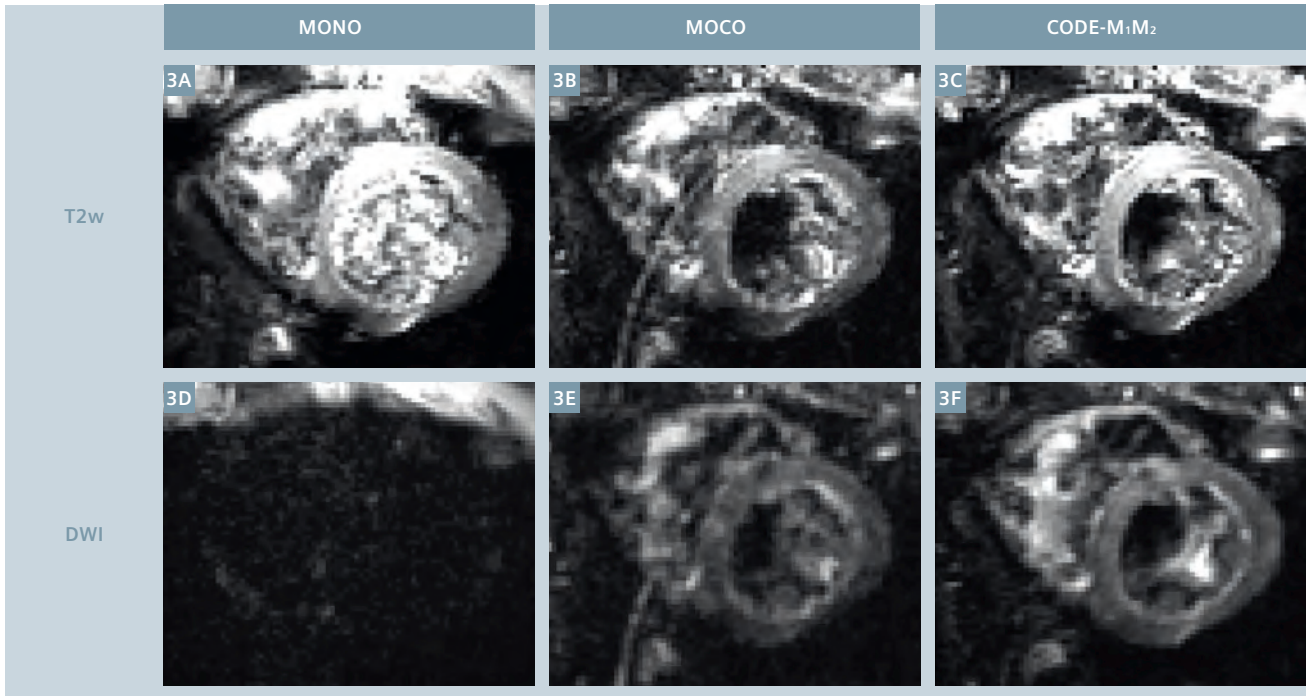
Methods

How are the diffusion encoding gradients designed?

Traditional diffusion encoding gradient waveform design uses an ad hoc approach that involves combining trapezoidal gradient waveforms with closed-form definitions that meet hardware constraints (G_{Max} and SR_{Max}) and ensure the desired properties (M_0, M_1, M_2, b-value), but are agnostic to changes in sequence timing. This tends to lead to inefficiencies in pulse sequence timing that can extend TEs (Fig. 2).

How did we optimize diffusion encoding gradients design?

A general approach to gradient design has been proposed [26] which uses numerical optimization to select the most time-efficient waveform that adheres to all hardware (G_{Max} and SR_{Max}), gradient waveform (M_0, M_1, M_2, b-value, etc.) and pulse sequence (field-of-view, bandwidth, resolution, etc.) constraints. This approach was recently used to design the fastest possible velocity encoding gradients for measuring through plane blood flow [27]. We have applied this concept to more efficiently encode diffusion in the beating heart using convex optimized diffusion encoding (CODE) gradients [28]. This approach calculates the diffusion encoding gradient waveform that minimizes TE for any spatial resolution (Fig. 2). By optimizing the diffusion encoding gradient waveform we can remove all diffusion encoding dead time and achieve M_1 and M_2 moment compensated diffusion encoding in shorter TEs than any previous method. This development permits bulk-motion



3 cDWI images with b = 0 **(3A–C)** and b = 350 s/mm² **(3D–F)** are shown for a healthy volunteer at a systolic cardiac phase with MONO, MOCO, and CODE. MONO cDWI had the highest SNR with b = 0 but were severely motion corrupted with diffusion encoding. MOCO and CODE were both robust to cardiac motion with b = 350 s/mm² but CODE had higher SNR due to its shorter TE.

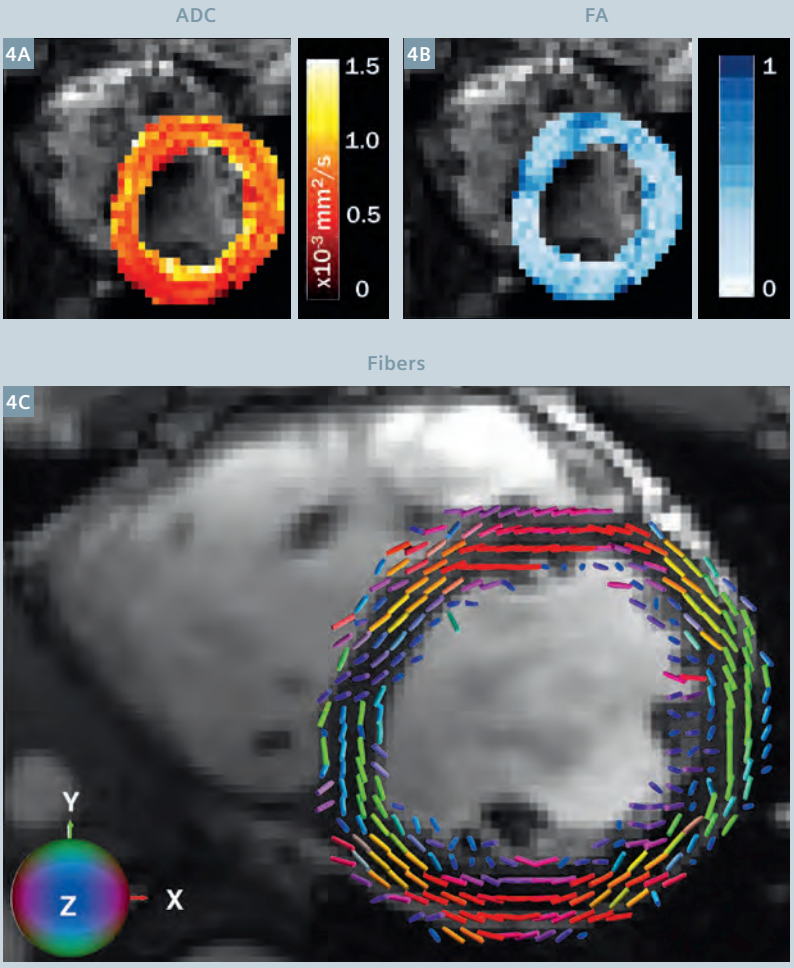
insensitive cDWI with 1.5 mm in-plane spatial resolution that matches clinical LGE MRI and enables cDWI to be a practical GBCA-free method for the clinical evaluation of MI.

How are CODE cDWI images acquired?

High resolution (1.5 x 1.5 x 5.0 mm) cDWI images (b = 350 s/mm²) were acquired in healthy volunteers on a 3T scanner (MAGNETOM Prisma) using three encoding schemes: monopolar (TE = 65 ms), non-optimized MOCO (TE = 93 ms) and CODE (TE = 76 ms) encoding. Diffusion was encoded along three orthogonal directions and three averages were acquired to improve image SNR. Imaging was performed under free breathing with navigator triggering (scan time: ~1 minute per technique). An additional CODE cDTI dataset was acquired with coarser resolution (2.5 x 2.5 x 5.0 mm) for fiber mapping (TE = 59 ms). This acquisition included six diffusion encoding directions and ten signal averages (scan time: ~10 minutes).

How does CODE cDWI compare with other approaches?

Monopolar cDWI resulted in dramatic bulk motion signal dropouts (Fig. 3) that were eliminated with MOCO and CODE. CODE also improved the SNR compared to conventional MOCO (Fig. 3). ADC, FA, and myocyte orientation maps were reconstructed from the CODE cDTI data and demonstrate the high SNR and high quality of the parametric and orientation maps (Fig. 4).



4 Apparent diffusion coefficient (ADC) maps **(4A)**, fractional anisotropy (FA) maps **(4B)** and superquadric glyph renderings of local myofiber orientation **(4C)** reconstructed from CODE cDWI in a healthy volunteer.

Discussion

We have developed, implemented, and demonstrated a novel approach to cDWI using convex optimized diffusion encoding (CODE) gradients. This approach is robust to cardiac bulk motion and enables sensitivity to diffusion in the beating heart. With the ability to routinely measure diffusion in the beating heart a number of quantitative imaging metrics become available. While the apparent diffusion coefficient (ADC) and the fractional anisotropy (FA) are the principal measures reported in the neuro literature, there are many additional metrics that may prove specifically useful in the heart [29]. In particular, measures of local myocyte coherence and/or disarray, and changes to myocyte and sheetlet orientations may provide exceptional insightful about myocardial function and dysfunction.

Future work will see broader application of CODE cDWI in both healthy volunteers and patients with a variety of clinical indications. Moving forward cDWI may lead directly to insights about microstructural organization in the healthy heart and may become a routine method for evaluating changes to cardiac microstructure without the need for GBCA. Central to the pursuit of this goal is a partnership between physicists and physicians that enables novel insights arising from the latest MRI technologies.

Acknowledgements

The authors are grateful to receive research support from the Department of Radiological Sciences at UCLA, the National Institutes of Health, the American Heart Association, and Siemens Healthcare.

References

1 Fisher D, Eberlein E. The New, High-Performance MR Gradient System XR 80/200. Design; Benefits and Safe Operation. MAGNETOM Flash 52 (2/2013): 160-163.

2 Atkinson DJ, Edelman RR. Cineangiography of the heart in a single breath hold with a segmented turboFLASH sequence. Radiology 1991;178(2):357-360.
3 Ennis DB, Kindlmann G. Orthogonal tensor invariants and the analysis of diffusion tensor magnetic resonance images. Magn Reson Med 2006;55(1):136-146.
4 Schlaug G, Siewert B, Benfield A, Edelman RR, Warach S. Time course of the apparent diffusion coefficient (ADC) abnormality in human stroke. Neurology 1997;49(1):113-119.
5 Hsu EW, Xue R, Holmes A, Forder JR. Delayed reduction of tissue water diffusion after myocardial ischemia. Am J Physiol 1998;275(2 Pt 2):H697-702.
6 Abdullah OM, Drakos SG, Diakos NA, Wever-Pinzon O, Kfoury AG, Stehlik J, Selzman CH, Reid BB, Brunisholz K, Verma DR, Myrick C, Sachse FB, Li DY, Hsu EW. Characterization of diffuse fibrosis in the failing human heart via diffusion tensor imaging and quantitative histological validation. NMR Biomed 2014;27(11):1378-1386.
7 Nguyen C, Fan Z, Xie Y, Dawkins J, Tseliou E, Bi X, Sharif B, Dharmakumar R, Marban E, Li D. In vivo contrast free chronic myocardial infarction characterization using diffusion-weighted cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2014;16:68.
8 Roger VL. Epidemiology of myocardial infarction. The Medical clinics of North America 2007;91(4):537-552; ix.
9 Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, Klocke FJ, Bonow RO, Judd RM. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 2000;343(20):1445-1453.
10 Kelle S, Roes SD, Klein C, Kokocinski T, de Roos A, Fleck E, Bax JJ, Nagel E. Prognostic value of myocardial infarct size and contractile reserve using magnetic resonance imaging. Journal of the American College of Cardiology 2009;54(19):1770-1777.
11 Flett AS, Hasleton J, Cook C, Hausenloy D, Quarta G, Ariti C, Muthurangu V, Moon JC. Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. JACC Cardiovascular imaging 2011;4(2):150-156.
12 Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW, American Heart Association Councils on Kidney in Cardiovascular Disease HBPRCC, Epidemiology, Prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension 2003;42(5):1050-1065.
13 LeGrice IJ, Hunter PJ, Smaill BH. Laminar structure of the heart: A mathematical model. Am J Physiol-Heart C 1997;272(5):H2466-H2476.
14 Costa KD, Takayama Y, McCulloch AD, Covell JW. Laminar fiber architecture and three-dimensional systolic mechanics in canine ventricular myocardium. Am J Physiol 1999;276(2 Pt 2):H595-607.
15 Hsu EW, Muzikant AL, Matulevicius SA, Penland RC, Henriquez CS. Magnetic resonance myocardial fiber-orientation mapping with direct histological correlation. Am J Physiol 1998;274(5 Pt 2):H1627-1634.
16 Kung GL, Nguyen TC, Itoh A, Skare S, Ingels NB, Jr., Miller DC, Ennis DB. The presence of two local myocardial sheet populations confirmed by diffusion tensor MRI and histological validation. J Magn Reson Imaging 2011;34(5):1080-1091.
17 Ferreira PF, Kilner PJ, McGill LA, Nielles-Vallespin S, Scott AD, Ho SY, McCarthy KP, Haba MM, Ismail TF, Gatehouse PD, de Silva R, Lyon AR, Prasad SK, Firmin DN, Pennell DJ. In vivo cardiovascular magnetic resonance diffusion tensor imaging shows evidence of abnormal myocardial laminar orientations and mobility in hypertrophic cardiomyopathy. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance 2014;16:87.
18 Dou J, Reese TG, Tseng WY, Wedeen VJ. Cardiac diffusion MRI without motion effects. Magn Reson Med 2002;48(1):105-114.
19 Fischer SE, Stuber M, Scheidegger MB, Boesiger P. Limitations of stimulated echo acquisition mode (STEAM) techniques in cardiac applications. Magn Reson Med 1995;34(1):80-91.
20 Gamper U, Boesiger P, Kozerke S. Diffusion imaging of the in vivo heart using spin echoes--considerations on bulk motion sensitivity. Magn Reson Med 2007;57(2):331-337.
21 Pai VM, Rapacchi S, Kellman P, Croisille P, Wen H. PCATMIP: enhancing signal intensity in diffusion-weighted magnetic resonance imaging. Magn Reson Med 2011;65(6):1611-1619.
22 Stoeck CT, von Deuster C, Genet M, Atkinson D, Kozerke S. Second-order motion-compensated spin echo diffusion tensor imaging of the human heart. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2015.
23 Welsh C, Di Bella E, Hsu E. Higher-Order Motion-Compensation for In Vivo Cardiac Diffusion Tensor Imaging in Rats. IEEE transactions on medical imaging 2015.
24 Nguyen C, Fan Z, Sharif B, He Y, Dharmakumar R, Berman DS, Li D. In vivo three-dimensional high resolution cardiac diffusion-weighted MRI: A motion compensated diffusion-prepared balanced steady-state free precession approach. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2013;72(5):1257-1267.
25 Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E, Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized P. Standardized cardiovascular magnetic resonance imaging (CMR) protocols, society for cardiovascular magnetic resonance: board of trustees task force on standardized protocols. J Cardiovasc Magn Reson 2008;10:35.
26 Hargreaves BA, Nishimura DG, Conolly SM. Time-optimal multidimensional gradient waveform design for rapid imaging. Magn Reson Med 2004;51(1):81-92.
27 Middione MJ, Wu HH, Ennis DB. Convex gradient optimization for increased spatio-temporal resolution and improved accuracy in phase contrast MRI. Magn Reson Med 2014;72(6):1552-1564.
28 Aliotta E, Wu HH, Ennis D. Convex Optimized Diffusion Encoding (CODE) Gradient Waveforms for Minimum Echo Time and Bulk Motion Compensated Diffusion Weighted MRI. Magnetic Resonance in Medicine 2016.
29 Kindlmann G, Ennis DB, Whitaker RT, Westin CF. Diffusion tensor analysis with invariant gradients and rotation tangents. IEEE Trans Med Imaging 2007;26(11):1483-1499.

Contact

Daniel B. Ennis, Ph.D.
University of California
Peter V. Ueberroth Building, Suite 1471, Room B
10945 Le Conte Avenue
Los Angeles, CA 90095, USA
Phone: +1 310 206 0713
Fax: +1 310 825 5837
daniel.ennis@ucla.edu