Evaluation of MyoStrain™ in Clinical Practice

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Investigators

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Purpose of Project

This study is designed to evaluate the use of MyoStrain cardiac MRI (CMR) pulse sequence to determine how the use of this single pulse sequence may alter treatment decisions and clinical outcomes in patients who are undergoing cardiac MRI. Strain Encoding (SENC) MRI technology is a rapid MRI scan providing detailed structural and functional imaging of the heart muscle, and is of great diagnostic value in guiding treatment decisions for patients with heart failure, drug toxicity (e.g. chemotherapy), and coronary artery disease. The goal is to determine if Myostrain CMR can detect subtle changes of heart damage earlier or with more sensitivity/specificity to ultimately improve patient outcomes and earlier intervention in their treatment course. The purpose is to determine if and how patients treatments are impacted (morbidity/mortality outcomes) as a result of using this SENC sequence, or if there is no significant difference between the current gold standard (regular cardiac MRI, ultrasound, or nuclear medicine heart scans).

Specific Objectives

- The primary objective is to evaluate the workflow for rapid MyoStrain testing in clinical practice, and its direct clinical impact in impacting clinical outcomes and changing therapeutic decision making by the treating physicians.
- The primary efficacy endpoint is the efficiency and accuracy of MyoStrain testing in obtaining global and segmental strain measurements including Global Circumferential Strain, Global Longitudinal Strain, Left Ventricular Ejection Fraction (LVEF), Mass, and Volumes. The workflow analysis will be performed by the investigators based on clinical experience compared to alternative imaging modalities.
- An additional primary efficacy endpoint will determine (quantitively) the ability of Myostrain to influence treatment decisions by earlier detection of progressive heart disease when compared to the current gold standards.

Rationale/Background

Device Description

The MyoStrain SENC CMR Imaging System is limited to observational evaluation within the United States. The MyoStrain system has European approval with an EC Certificate according to Directive 93/42/EEC on Medical Devices, Annex II excluding Section 4 (CE 657862) in respect of: Design, development and manufacture of software for the quantification of cardiac MRI images.

Strain Encoding (SENC) MRI technology is a fast MRI scanning diagnostic test that measures the contraction of the heart muscle in one to three heartbeat(s) per image plane, depending on the specific pulse sequence and associated MRI Manufacturer Scanner type and software version. This means that patients can be scanned very fast, in many cases while breathing, and a complete view of the ventricles' health can be obtained in less than a minute. Quantitative assessment of the strength of the heart muscle can have many clinical applications, but its highest value is in the two largest heart disease populations: those patients with heart failure and coronary artery disease.

SENC is an MRI Pulse Sequence for Strain Encoding

- A pulse sequence is an algorithm that instructs the MRI scanner to acquire certain types of images. Any MRI scanner has a large number of pulse sequences for general and specialized imaging of different parts of the body. They produce images that show different anatomies, physiologies, or pathologies of the different tissues of the body. For imaging the heart, there is a group of specialized pulse sequences that can show different aspects of the heart, including, but not limited to, the structure of the heart, the motion of the heart, the tissue characterization of the muscle, the flow of the blood, the structure of the vessels, and more.
- The Strain Encoding (SENC) pulse sequence is a specialized pulse sequence that produces images of the heart muscle that reveal the underlying contraction of the muscle of a healthy heart and associated weaknesses in case of disease. The measurements of the deformations of regions within the heart muscle ("myocardium") associated by contraction and relaxation during a single heartbeat is measured by the mechanical quantity called "strain."
- Myocardial Solutions, Inc. software measures tissue deformation or "strain" from the pulse sequence images. Quantitatively, "strain" is a mechanical property of deforming objects and measured as the percentile change in spacing between two points on a deforming object. For example, when muscle contracts, the muscle length is shortened. For example, a 30% shortening of the muscle is measured as strain of negative 30%.
- Measuring the shortening of the Heart Muscle results in two parameters that SENC quantifies: circumferential and longitudinal strain. Strain measurement depends on "direction" of measuring. For measuring the contraction of the heart muscle, there are two main directions that are typically used: 1) longitudinal strain, which describes the contraction of the myocardium that contributes to the base-to-apex contraction of the heart chambers; 2) circumferential strain, which describes the contraction of heart muscle fibers around the circumference of the chambers of the heart.

- Using SENC, circumferential and longitudinal strain values in 37 regions are measured in less than 2 minutes.

The Intended Use of the MyoStrain SENC MRI acquisition is:

- MyoStrain SENC software receives image data from MRI storage archives and performs viewing, image manipulation, communication, printing, and quantification of images. Available measurements include longitudinal and circumferential strain to quantitatively describe the wall motion of the heart. Tools are provided for display of regional motion properties of the heart.
- This unique sequence (SENC) will be used as an add-on to already-ordered cardiac MRI in many clinical scenarios (heart-failure, chemotherapy-related heart toxicity, inflammatory conditions such as sarcoid) to detect earlier progression or new heart-disease, that will change the management of patients (e.g. decreasing the amount of chemotherapy, changing chemotherapy regiment, or adding new cardiac failure drugs to prevent further decline or improve heart function).
- A report interface is provided. Measurement tools provide information that can be output in standardized or specialized report formats. This interface makes it possible to quickly and reliably fill out a complete clinical report of a cardiac imaging exam with strain. The results of the measurement tools are interpreted by the physician and can be communicated to referring physicians to support the determination of a diagnosis.

Clinical & Preclinical Testing

Myocardial Solutions, Inc. (MSI) SENC Software was implemented with SENC MRI acquisition using source codes that were developed at Johns Hopkins University. Both Diagnosoft before and MSI today continue to use the original SENC strain source code. SENC pulse sequences, derived from the SENC source code, designed for Philips, Siemens, and GE MRI Scanners, have been validated with phantom models, and clinical testing.

The MSI software leverages prior SENC image acquisition and processing functions that have been extensively studied on volunteers, phantoms studies, and clinical applications. The Fast SENC software processes images obtained with the well-studied SENC pulse sequence, which has supported several publications demonstrating the utility of strain imaging for various clinical applications.

Implementation of the SENC MRI acquisition in the Myocardial Solutions SENC Software has been validated as evidenced by literature across three separate comparisons: Comparisons with 1) Diagnosoft HARP, a 510k FDA certified software for measuring strain from tagged MR images; 2) EchoPAC STE, a certified software from GE Vingmed for measuring strain using speckle tracking methods; and 3) various physiological and pathological indicators.

Validation of SENC relative to Diagnosoft HARP

- Diagnosoft HARP is a 510k certified software for the analysis of MR Tagging images of the heart and measuring the strain that reveals the deformation of the myocardium as the heart muscle contracts and relaxes. Diagnosoft HARP is considered to be the gold standard for measuring regional strain and there are over 100 peer-reviewed published studies on the use of strain from HARP.
- Published Comparisons: SENC versus Diagnosoft HARP compared the strain measurements from SENC to strain calculated by MR Tagging and Diagnosoft HARP software. [1] [2] [3] The comparisons showed strong correlation in measurements of strain, both regional and global, and also the different strain measurements, such as longitudinal and circumferential strain; the correlation between SENC and tagged MRI was significant with R=0.90.
- The published literature demonstrates that SENC strain measurements are comparable to those obtained used MR Tagging and HARP software, which is the gold standard method for measuring strain.

Comparison of SENC to EchoPAC, GE Vingmed STE

- EchoPAC is a 510k and CE Mark certified package form GE Vingmed for the processing of echocardiographic images and films. It can measure the deformation and strain of tissue using speckle tracking echocardiography (STE), which is an image post-processing algorithm.
- Published Comparisons: SENC versus EchoPAC STE compares the strain measurements from SENC to the strain calculated using Tissue Strain Echocardiography (STE). [4] STE was calculated using EchoPAC software from GE.
- Cardiac MRI measurements of strain using SENC and MR tagging are considered to be equivalent to STE or better due to the excellent image of cardiac tissue by MRI and creation of actual physical markers inside the tissue to measure strain. STE is an image processing method that tries to extract motion and strain from conventional echocardiographic movies with their known image quality limitations.
- The published comparisons showed a correlation between strain measurements obtained by SENC and those calculated by STE. It is important to point out that MRI, as a gold standard method, was used as the reference for measuring strain. STE post-processing calculations were expected to be inherently inferior as it inherits some of the suboptimal image qualities of echocardiography (relative to MRI).

Validation of SENC MyoStrain Based on Clinical Physiological and Pathological Indicators

- SENC strain was directly compared to different physiological and pathological indicators to understand the mechanics of the heart muscle and alterations due to underlying disease and pathology. This includes the understanding of the contraction of the left and right ventricles, changes in strain in the case of myocardial infarction as determined using delayed enhancement methods, and detection of ischemia in patients by utilizing stress testing.

- Published Comparisons: SENC Strain for Physiological and Pathological Indicators. Different studies were done using SENC to understand the mechanics of the heart wall muscle and the changes that accompany certain diseases. In the case of coronary artery diseases, the studies showed changes in strain because of acute coronary artery syndrome that results in myocardial infarction. Strain also detected ischemia when combined with stress, detecting ischemia at lower stress levels compared to stress CINE MRI.
- Stress testing for ischemia, performed on patients with suspected or know ischemic heart disease, demonstrated that measured strain was more sensitive in detecting stenosis in the coronary arteries compared to 1) conventional cine movies with qualitative assessment of abnormal wall motion under stress, and 2) the outcomes of revascularization of positively diagnosed patients. [5] [6] [7] [8] [9]
- Myocardial infarction studies show the value of strain measurements in assessing, with high accuracy, changes in regional function associated with damage from myocardial infarction. [10] [11] [12] [13] Quantification of changes in contraction is more accurate (more sensitive and specific) in associating with the depth of damage vis-à-vis subjective wall motion assessment.
- Cardiac mechanics studies illustrated other applications of SENC strain measurements in understanding the mechanics of the heart, especially the left and right ventricles. [14] [15] [16] [17] [18] These healthy subjects studies demonstrated, with high accuracy and precision, the ability to detect subtle variations in regional contraction. Also, quantification revealed variations in contractility as a result of diseases affecting the right ventricle, which is very hard to assess using echocardiography because of the position of the right ventricle close to the ribs and the sternum and its geometry.

Methodology

This prospective study will include up to 100 patients who will be enrolled based on meeting the stated inclusion/exclusion criteria. Upon completion of the informed consent, patients will undergo SENC MyoStrain testing in a Siemens Manufacturer Scanner with a validated pulse sequence. The testing will incorporate baseline MyoStrain Testing in which 3 short axis slices and 3 long axis slices will be planned for imaging and then recorded with MyoStrain testing.

System setup and testing methodology will follow the Myocardial Solutions SENC User's Manual 4.x. The SENC MyoStrain Test procedure is a quick and simple analysis which will require only one series of images. The importation of the images from the scanner and organization of these images is mostly automated and requires very minimal interaction to function correctly. The workflow of the SENC MyoStrain test requires only one scan and analysis phase allowing the complete scan to be completed within 2 minutes after imaging planning.

Data obtained for the clinical and research scan will be stored in PACS. KUMC will provide the first 20 de-identified MyoStrain raw images and outcome reports to MyoCardial Solutions**.**

Inclusion Criteria

- Patients already scheduled for diagnostic testing with commercially available imaging modality (cardiac MRI)
- The patient population will include (but not limited to), those being evaluated for heart disease and heart failure that may be related to vascular disease (coronary artery disease), drug related heart failure (chemotherapy, alcohol), inflammatory systemic conditions (sarcoidosis, amyloidosis, lupus), myocarditis, and/or infectious etiologies
- Provided written informed consent

Exclusion Criteria

- Contraindication to Magnetic Resonance Imaging

Risks

The SENC MyoStrain software with the associated MRI Manufacturer Scanner pulse sequence is a noninvasive imaging technology. There is minimal direct physical risk for imaged subjects as it is an MRI procedure that does not require any invasive intervention or injections. As such the risks are limited to those typical for conventional non-contrast (e.g. without contrast injection) MRI exams. Subjects will be evaluated as an inclusion criteria for potential contraindications to MRI imaging. Considering image acquisition is very fast (< 5 min) reducing time within the magnetic bore, risks of claustrophobia or anxiety may be reduced compared to traditional MRI tests.

The MSI SENC MyoStrain software has been tested and validated following ISO 14971 (Medical Devices – Application of Risk Management to Medical Devices).

Detailed risk assessments have been done by Myocardial Solutions, Inc. throughout the software development. The company routinely performs management review that include analysis of device performance, change control (design, process, labeling), and corrective and preventative action for the product.

Myocardial Solutions' risk assessment has been completed and clinical risks have been reduced as far as possible by device design, labeling, and training protocols for intended users. There are no unacceptable residual clinical risks based on the risk/benefit reviews.

Data Management

Data obtained for the clinical and research scan will be stored in PACS. KUMC will provide the first 20 de-identified MyoStrain raw images and outcome reports to MyoCardial Solutions to ensure quality control and technologist certification. In addition, up to five scans may be requested quarterly to ensure technologist proficiency.

References

[1] G. Korosoglou, A. A. Youssef, K. C. Bilchick, E.-S. Ibrahim, A. C. Lardo, S. Lai and N. F. Osman, "Real-Time Fast Strain-Encoded Magnetic Resonance Imaging to Evaluate Regional Myocardial Function at 3.0 Tesla: Comparison to Conventional Tagging," Journal of Magnetic Resonance Imaging, vol. 27, no. 5, pp. 1012-1018, May 2008.

[2] H. Sugimori, N. Oyama-Manabe, K. Ishizaka, H. Hamaguchi and M. Sakata, "Comparison of SPAMM and SENC Methods for Evaluating Peak Circumferential Strain at 3T," Magnetic Resonance Medical Science, vol. 12, no. 1, pp. 69-75, 2013.

[3] Y. Ohyama, B. Ambale-Venkatesh, E. Chamera, M. L. Shehata, C. P. Corona-Villalobos, S. L. Zimmerman, P. M. Hassoun, D. A. Bluemke and J. A. Lima, "Comparison of Strain Measurement from Multimodality Tissue Tracking with Strain-Encoding MRI and Harmonic Phase MRI in Pulmonary Hypertension," International Journal of Cardiology, vol. 182, pp. 342-348, 2015.

[4] E. Altiok, M. Neizel, S. Tiemann, V. Krass, M. Becker, C. Zwicker, R. Koos, M. Kelm, N. Kraemer, F. Schoth, N. Marx and R. Hoffmann, "Layer-Specific Analysis of Myocardial Deformation for Assessment of Infarct Transmurality: Comparison of Strain-Encoded Cardiovascular Magnetic Resonance with 2D Speckle Tracking Echocardiography," European Heart Journal - Cardiovascular Imaging, vol. 14, pp. 570-578, 2013.

[5] G. Korosoglou, G. Gitsioudis, A. Voss, S. Lehrke, N. Riedle, S. J. Buss, C. Zugck, E. Giannitsis, N. F. Osman and H. A. Katus, "Strain-Encoded Cardiac Magnetic Resonance During High-Dose Dobutamine Stress Testing for the Estimation of Cardiac Outcomes: Comparison to Clinical Parameters and Conventional Wall Motion Readings," Journal of American College of Cardiology, vol. 58, no. 11, pp. 1140-9, 2011.

[6] G. Korosoglou, S. Lehrke, A. Wochele, B. Hoerig, D. Lossnitzer, H. Steen, E. Giannitsis, N. F. Osman and H. A. Katus, "Strain-Encoded CMR for the Detection of Inducible Ischemia During Intermediate Stress," JACC Cardiovascular Imaging, vol. 3, no. 4, pp. 361-371, 2010.

[7] G. Korosoglou, D. Lossnitzer, D. Schellberg, A. Lewien, A. Wochele, T. Schaeufele, M. Neizel, H. Steen, E. Giannitsis, H. A. Katus and N. F. Osman, "Strain-Encoded Cardiac Magnetic Resonance Imaging as an Adjunct for Dobutamine Stress Testing. Incremental Value to Conventional Wall Motion Analysis," Circulation Cardiovascular Imaging, vol. 2, no. 2, pp. 132-140, 2009.

[8] G. Korosoglou, S. Fetterer, P. M. Humpert, N. Riedle, D. Lossnitzer, B. Hoerig, H. Steen, E. Giannitsis, N. F. Osman and H. A. Katus, "Strain-Encoded Cardiac MR During High-Dose Dobutamine Stress Testing: Comparison to Cine Imaging and to Myocardial Tagging," Journal of Magnetic Resonance Imaging, vol. 29, no. 5, pp. 1053-1061, May 2009.

[9] G. Korosoglou, S. Giusca, G. Gitsioudis, C. Erbel and H. A. Katus, "Cardiac Magnetic Resonance and Computed Tomography Angiography for Clinical Imaging of Stable Coronary Artery Disease. Diagnostic Classification and Risk Stratification," Frontiers in Physiology, vol. 5, pp. 1-18, 06 August 2014.

[10] M. Neizel, G. Korosoglou, D. Lossnitzer, H. Kuhl, R. Hoffmann, C. Ocklenburg, E. Giannitsis, N. F. Osman, H. A. Katus and H. Steen, "Impact of Systolic and Diastolic Deformation Indexes Assessed by Strain-Encoded Imaging to Predict Persistent Severe Myocardial Dysfunction in Patients After Acute Myocardial Infarction at Follow-Up," Journal of the American College of Cardiology, vol. 56, no. 13, pp. 1056-1062, 2010.

[11] M. Neizel, D. Lossnitzer, G. Korosoglou, T. Schaufele, H. Peykarjou, H. Steen, C. Ocklenburg, E. Giannitsis, H. A. Katus and N. F. Osman, "Strain-Encoded MRI for Evaluation of Left Ventricular Function and Transmurality in Acute Myocardial Infarction," Circulation Cardiovascular Imaging, vol. 2, pp. 116-122, 2009.

[12] R. Koos, E. Altiok, J. Doetsch, M. Neizel, G. Krombach, N. Marx and R. Hoffmann, "Layer-Specific Strain-Encoded MRI for the Evaluation of Left Ventricular Function and Infarct Transmurality in Patients with Chronic Coronary Artery Disease," International Journal of Cardiology, vol. 166, no. 1, pp. 85-89, 5 June 2013.

[13] N. Oyama-Manabe, N. Ishimori, H. Sugimori, M. Van Cauteren, K. Kudo, O. Manabe, T. Okuaki, T. Kamishima, Y. M. Ito, H. Tsutsui, K. K. Tha, S. Terae and H. Shirato, "Identification and Further Differentiation of Subendocardial and Transmural Myocardial Infarction by Fast Strain-Encoded (SENC) Magnetic Resonance Imaging at 3.0 Tesla," European Radiology, vol. 21, no. 11, pp. 2362-2368, November 2011.

[14] A. Youssef, E.-S. H. Ibrahim, G. Korosoglou, M. R. Abraham, R. G. Weiss and N. F. Osman, "Strain-Encoding Cardiovascular Magnetic Resonance for Assessment of Right-Ventricular Regional Function," Journal of Cardiovascular Magnetic Resonance, vol. 10, no. 33, pp. 1-10, 2008.

[15] M. L. Shehata, T. A. Basha, W. H. Tantawy, J. A. Lima, J. Vogel-Claussen, D. A. Bluemke, P. M. Hassoun and N. F. Osman, "Real-Time Single-Heartbeat Fast Strain-Encoded Imaging of Right Ventricular Regional Function: Normal Versus Chronic Pulmonary Hypertension," Magnetic Resonance in Medicine, vol. 64, pp. 98-106, 2010.

[16] A. Hamdan, T. Thouet, S. Kelle, I. Paetsch, R. Gebker, E. Wellnhofer, B. Schnackenburg, A. S. Fahmy, N. F. Osman and E. Fleck, "Regional Right Ventricular Function and Timing of Contraction in Healthy Volunteers Evaluated by Strain-Encoded MRI," Journal of Magnetic Resonance Imaging, vol. 28, no. 6, pp. 1379-1385, December 2008.

[17] A. Hamdan, T. Thouet, S. Kelle, E. Wellnofer, I. Paetsch, R. Gebker, B. Schnackenburg, A. S. Fahmy, N. F. Osman, A. Bornstedt and E. Fleck, "Strain-Encoded MRI to Evaluate Normal Left Ventricular Function and Timing of Contraction at 3.0 Tesla," Journal of Magnetic Resonance Imaging, vol. 29, no. 4, pp. 799-808, April 2009.

[18] B. H. Freed, W. Tsang, N. M. Bhave, A. R. Patel, L. Weinert, M. Yamat, B. M. Vicedo, K. Dill, V. Mor-Avi, M. Gomberg-Maitland and R. M. Lang, "Right Ventricular Strain in Pulmonary Arterial

Hypertension: A 2D Echocardiography and Cardiac Magnetic Resonance Study," Echocardiography, vol. 32, no. 2, pp. 257-263, Feb 2015.