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Estimation of myocardial fibrosis in humans with dual energy CT

Vidhya Kumar[a], Thura T. Harfi[a], Xin He[b], Beth McCarthy[a], Andrea Cardona[a], Orlando P. Simonetti[a], Subha V. Raman[a,*]

[a] The Ohio State University Davis Heart and Lung Research Institute, 473 W. 12th Ave, Columbus, OH, 43210, USA
[b] University of Maryland School of Public Health, Department of Epidemiology and Biostatistics, College Park, MD, 20742, USA

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ABSTRACT

Background: The current clinical standard for *in vivo* imaging of myocardial fibrosis is contrast-enhanced cardiac magnetic resonance (CMR). We sought to validate a novel non-contrast dual energy computed tomography (DECT) method to estimate myocardial fibrosis in patients undergoing CMR with contrast.

Methods: All subjects underwent non-contrast, prospectively-triggered cardiac DECT on a single source scanner with interleaved acquisition between tube voltages of 80 and 140 kVp. Monochromatic images were reconstructed at 11 energies spanning 40–140 keV; a region of interest (ROI) was drawn in the mid-inferoseptal segment, recording mean attenuation value in the ROI, at each energy level. Comparison was made to data from single energy (70 keV) image data. Linear discriminant analysis (LDA) was performed to compare the predictive capability of single vs. multi-energy inferoseptal segment CT attenuation on myocardial fibrosis by both visually assessed LGE (absent/present fibrosis) and CMR T1 mapping-derived myocardial extracellular volume fraction (ECV).

Results: The multi-energy CT/LDA approach performed better than a single energy approach to discriminate among LGE-CMR classes of present/absence myocardial fibrosis severity, demonstrating correct classification rates of 89% and 71%, respectively. The multi-energy CT/LDA approach also performed better in correctly discriminating normal from elevated ECV, doing so in 89% of patients vs. correct distinction of normal/elevated ECV in only 70% using the single energy approach.

Conclusions: Non-contrast cardiac DECT with multi-energy analysis better classifies myocardial fibrosis and extracellular volume compared to what is feasible with non-contrast single energy cardiac CT. These data support further evaluation of this approach to noninvasively assess myocardial fibrosis.

1. Introduction

Myocardial fibrosis is a pathologic condition that is substrate for arrhythmias, impairs cardiac contractility and relaxation, and may eventually contribute to heart failure and sudden cardiac death. The prevalence of left ventricular myocardial fibrosis is high in patients with heart failure[1] and cardiomyopathies[2,3] as well as those at high-risk for arrhythmias.[4] Accurate techniques for detection, estimation and quantification of myocardial fibrosis help insure appropriate diagnosis and treatment planning. Currently, contrast-enhanced cardiac magnetic resonance (CMR) is the clinical standard for noninvasive myocardial fibrosis imaging. However, impaired renal function, presence of non-MR compatible implants, and claustrophobia preclude CMR examination in a number of patients with suspected myocardial disease.

A noncontrast CT approach would be potentially appealing to assess myocardial fibrosis given feasibility in patients with contraindications to contrast-enhanced CMR. We have developed a non-contrast dual-energy CT with multi-energy analysis method, with promising pre-clinical data supporting ability to predict severity of myocardial fibrosis in a mouse model of hypertensive heart disease with diffuse fibrosis.[5] In this work, we implemented a similar non-contrast DECT approach with multienergy data analysis in human subjects, hypothesizing that such an approach could: 1) predict myocardial fibrosis in human subjects *in vivo* and 2) perform better than single-energy CT techniques for characterization of myocardial fibrosis.

2. Methods

2.1. Subject recruitment & enrollment

Twenty-eight subjects were enrolled in this study (Table 1). Patients ≥18 years of age clinically referred for CMR with myocardial T1

* Corresponding author. The Ohio State University, 473 W. 12th Ave, Suite 200, Columbus, OH, 43210, USA.
E-mail address: raman.1@osu.edu (S.V. Raman).

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Table 1
Study population.

Variable	Value
Age, years	58 ± 13
Male, N (%)	14 (50)
Body mass index, kg/m^2	27.9 ± 5.4
Diabetes, N (%)	4 (14)
Current or former smoker, N (%)	11 (39)
Hypertension, N (%)	15 (54)
Cardiac magnetic resonance indication, N (%)	
chest pain	6 (21)
cardiomyopathy	16 (57)
left ventricular hypertrophy	3 (11)
viability	3 (11)

mapping and late gadolinium enhancement (LGE) imaging at a single center (Ohio State University Richard M. Ross Heart Hospital) were prospectively screened for enrollment. Excluded were those unwilling to undergo a single noncontrast cardiac CT scan, as written informed consent was obtained in all participants in this institutional review board-approved study.

2.2. Image acquisition

Subjects underwent prospectively-triggered cardiac CT on a 64-slice multi-detector, single source scanner with kVp switching capabilities yielding interleaved acquisition between 80 and 140 kVp (750HD, GE Healthcare, Waukesha, WI). Images were acquired with detector coverage of 40 mm, slice thickness of 2.0 mm and matrix size of 512 in gemstone spectral imaging (GSI) mode.[6] Clinically-acquired CMR was performed on a 1.5T scanner (MAGNETOM Avanto, Siemens Medical Solutions, Malvern, PA). LGE was acquired 12–15 min post-intravenous administration of gadolinium-based contrast agent (gadobutrol 0.15 mmol/kg) in short-axis and long axis cardiac planes with appropriate inversion time selection.[7] Pre-contrast and post-LGE contrast T1 mapping used a modified look-locker pulse sequence (MOLLI)[8] in the identical mid-short axis plane.

2.3. Image processing and analysis

All images were analyzed by experienced staff blinded to clinical information. Two experienced readers provided consensus review of LGE images, assigning the mid-inferoseptal segment as LGE positive or negative. Myocardial and blood T1 values were recorded from pre- and post-contrast T1 maps, using a region of interest (ROI) within the mid-inferoseptal segment[9] for myocardial values and ROI within the LV cavity for blood values. Extracellular volume fraction (ECVcmr) was calculated using the following formula and hematocrit value recorded at the CMR exam, using 29% as a cutoff for normal[10]:

$$ECVcmr = 100 * (1 - hematocrit) * \frac{\left(\frac{1}{T1_{tissue,post-contrast}} - \frac{1}{T1_{tissue,native}}\right)}{\left(\frac{1}{T1_{blood,post-contrast}} - \frac{1}{T1_{blood,native}}\right)}$$

DECT images were post-processed and analyzed using GE's AW software, which provides monochromatic reconstructions over the range of 40–140 keV in 10 keV increments using the material decomposition method. Multiplanar reformatting was performed to generate a mid-short axis DECT image comparable to the mid-short axis plane by CMR. For each subject, and ROI drawn in the mid-inferoseptal myocardial segment – consistent with CMR myocardial postprocessing guidelines[11] - yielded attenuation values (Hounsfield units, HU) at each energy level that could be exported for further computational analysis. A second level of post-processing was performed in Matlab to remove pixels containing with HU < -1000 (e.g. fat) or > 300 (e.g. calcium). Finally, mean and standard deviation of CT attenuation values at each energy value were calculated for the mid-inferoseptal myocardium.

2.4. Analysis

All statistical analysis was performed with STATA v12.0 (College Station, TX). Multivariate analysis of variance (MANOVA) was performed to assess whether the mean CT attenuation values differed between LGE-negative vs. LGE-positive individuals or between normal ECV ($< 29\%$) and abnormal ECV ($\geq 29\%$)[12] groups.

Linear discriminant analysis (LDA) was the main statistical tool used for classification of enhancement and ECV in the inferoseptal segment.[13] LDA was performed using the post-processed mean CT attenuation value obtained from ROI measurements for each enrolled patient as described in prior work.[5] Briefly, LDA tested the ability of single energy (70 keV) values, multi-energy predictors, CT attenuation values, to correctly discriminate between fibrosis severity classes determined by qualitative expert review of LGE images and between normal/abnormal quantitative ECV. Preliminary testing of classifiers was performed using a prospective LDA method, which returned a predicted grouping based on CT characteristics for each enrolled

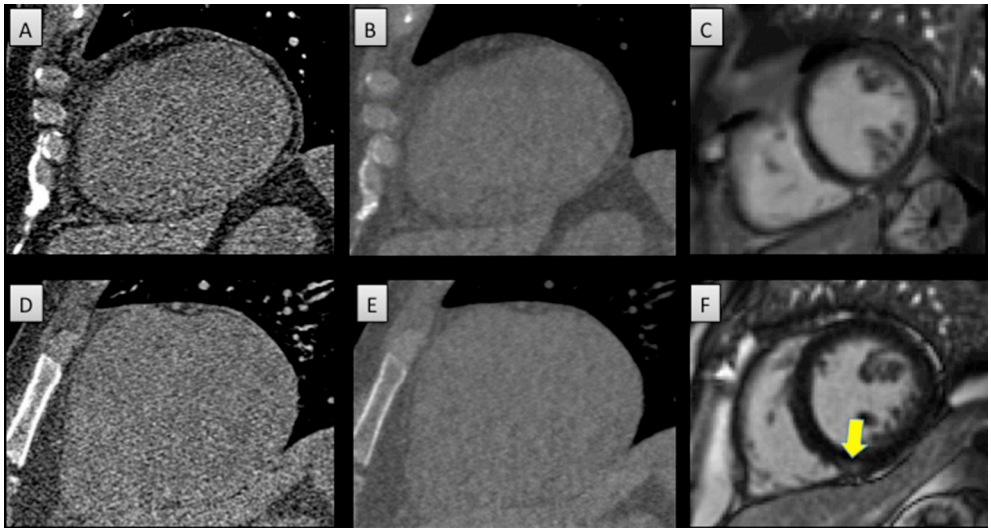

Fig. 1. Visual analysis of monochromatic images (e.g. 40 and 120 keV) from duel energy computed tomography (DECT) does not readily distinguish absent (Panels A–C) vs. present (Panels D–F) myocardial fibrosis as seen by late gadolinium enhancement cardiac magnetic resonance (LGE-CMR).

Table 2
Noncontrast DECT attenuation values across reconstructed energy levels by LGE group.

	40 keV	50	60	70	80	90	100	110	120	130	140
LGE-negative	57.7 ± 34.2	52.9 ± 19.2	47.3 ± 11.5	44.4 ± 7.0	45.6 ± 6.0	46.1 ± 7.6	45.6 ± 8.6	45.2 ± 9.4	44.9 ± 10.0	44.7 ± 10.5	44.5 ± 10.9
LGE-positive	50.2 ± 21.1	44.6 ± 13.8	40.4 ± 9.6	38.0 ± 8.6	37.3 ± 7.4	36.7 ± 7.3	36.1 ± 7.3	35.6 ± 7.4	35.3 ± 7.5	35.1 ± 7.6	34.9 ± 7.7

Table 3
Noncontrast DECT attenuation values across reconstructed energy levels by ECV group.

	40 keV	50	60	70	80	90	100	110	120	130	140
ECV < 29%	56.7 ± 22.9	49.8 ± 15.4	44.5 ± 9.9	41.4 ± 7.3	40.7 ± 7.3	40.0 ± 7.7	39.3 ± 7.5	38.7 ± 7.5	38.3 ± 7.5	38.0 ± 7.5	37.8 ± 7.5
ECV ≥ 29%	47.7 ± 27.3	44.1 ± 15.5	40.2 ± 10.6	38.2 ± 9.3	38.9 ± 8.3	38.9 ± 9.2	38.5 ± 10.0	38.3 ± 10.7	38.0 ± 11.2	37.9 ± 11.6	37.8 ± 11.9

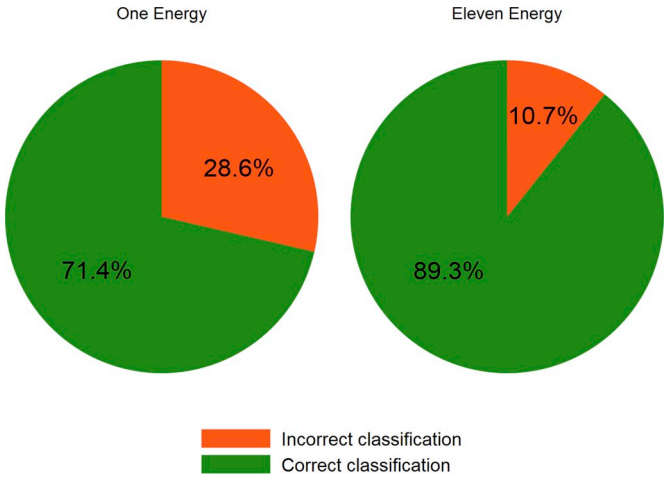

Fig. 2. Results of LDA to discriminate between presence vs. absence of myocardial fibrosis by late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) are shown, with greater accuracy using information across 11 energies vs. single energy analysis.

patient. Correct and incorrect classification rates were calculated as a proportion of total data.

3. Results

Twenty-eight patients, age 58 ± 13 years and 50% male, were prospectively enrolled to undergo DECT prior to clinically-acquired CMR. Body weight averaged 83.3 ± 21.9 kg. Cardiomyopathy was the most common indication for CMR in this cohort (Table 1). Myocardial fibrosis was visually apparent by LGE-CMR in 19 (68%, Fig. 1). Nine patients had myocardial ECV exceeding the 29% threshold for normal ECV. Average effective radiation dose per noncontrast cardiac DECT scan was 4.7 ± 0.68 mSv, and all DECT image sets were adequate in image quality for analysis. Attenuation values across monochromatic reconstructions are tabulated by LGE and ECV status in Tables 2 and 3.

MANOVA using attenuation values alone did not distinguish between LGE-positive and LGE-negative patients, or between normal ECV and abnormal ECV patients.

Single and multi-energy LDA analysis using the presence or absence of myocardial fibrosis defined by LGE as a grouping variable returned correct classification rates of 71% and 89%, respectively (Fig. 2). Single and multi-energy LDA analysis using normal/abnormal ECV as a grouping variable returned correct classification rates of 70% and 89%, respectively.

4. Discussion

Using a novel multienergy analysis approach derived from noncontrast cardiac DECT images, we have shown in a pilot cohort of patients that this method is superior to single energy-based acquisition and analysis in classifying presence or absence of discrete myocardial fibrosis and diffuse interstitial expansion by CMR. This was achieved with a radiation dose for the dual-energy acquisition in the range of noncontrast cardiac CT scans for coronary calcium scoring or contrast-enhanced myocardial perfusion CT scans. With our prior work showing that DECT yields comparable coronary artery calcium scores as usual single energy scan protocols,[14] the current work further advances the potential utility of noncontrast cardiac DECT for myocardial fibrosis assessment. We note that the acquisition technique produced images of sufficient quality to perform multi-energy analysis in normal to obese individuals, an important consideration in the cardiovascular patient population.

While encouraging, these first-in-man findings have some limitations. With our data showing an acceptable radiation dose in a small cohort, a larger trial can be considered. Also, we sought to characterize myocardial fibrosis, noting extensive histopathological validation of the midwall late gadolinium enhancement as representing discrete fibrosis, and growing data supporting increased ECV as a measure of diffuse interstitial fibrosis. However, it is possible that the myocardial differences between groups resulted from something other than collagen deposition. This method can be applied in further studies of other potential contributors to myocardial enhancement and interstitial expansion and their noncontrast multienergy DECT signatures.

5. Conclusion

A novel, noncontrast cardiac DECT-based method of analyzing attenuation values across multiple energies can accurately estimate myocardial fibrosis compared to established CMR techniques. Ability to noninvasively distinguish between presence and absence of fibrosis support further studies of noncontrast cardiac DECT for myocardial characterization.

Conflicts of interest and source of funding

The authors have no relevant financial conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2018.12.004.

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