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Original Research Article

3D left ventricular extracellular volume fraction by low-radiation dose cardiac CT: Assessment of interstitial myocardial fibrosis

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ABSTRACT

Background: Myocardial fibrosis leads to impaired cardiac function and events. Extracellular volume fraction (ECV) assessed with an iodinated contrast agent and measured by cardiac CT may be a useful noninvasive marker of fibrosis.
Objective: The purpose of this study was to develop and evaluate a 3-dimensional (3D) ECV calculation toolkit (ECVTK) for ECV determination by cardiac CT.
Methods: Twenty-four subjects (10 systolic heart failure, age, 60 ± 17 years; 5 diastolic failure, age 56 ± 20 years; 9 matched healthy subjects, age 59 ± 7 years) were evaluated. Cardiac CT examinations were done on a 320-multidetector CT scanner before and after 130 mL of iopamidol (Isovue-370; Bracco Diagnostics, Plainsboro, NJ, USA) was administered. A calcium score type sequence was performed before and 7 minutes after contrast with single gantry rotation during 1 breath hold and single cardiac phase acquisition. ECV was calculated as $(\Delta HU_{myocardium}/\Delta HU_{blood}) \times (1 - Hct)$ where Hct is the hematocrit, and ΔHU is the change in Hounsfield unit attenuation $= HU_{after\ iodine} - HU_{before\ iodine}$. Cardiac magnetic resonance imaging was performed to assess myocardial structure and function.
Results: Mean 3D ECV values were significantly higher in the subjects with systolic heart failure than in healthy subjects and subjects with diastolic heart failure (mean, 41% ± 6%, 33% ± 2%, and 35% ± 5%, respectively; $P = 0.02$). Interobserver and intraobserver agreements were excellent for myocardial, blood pool, and ECV (intraclass correlation coefficient, >0.90 for all). Higher 3D ECV by cardiac CT was associated with reduced systolic circumferential strain, greater end-diastolic and -systolic volumes, and lower ejection fraction ($r = 0.70$, $r = 0.60$, $r = 0.73$, and $r = -0.68$, respectively; all $P < 0.001$).
Conclusion: 3D ECV by cardiac CT can be performed with ECVTK. We demonstrated increased ECV in subjects with systolic heart failure compared with healthy subjects. Cardiac CT results also showed good correlation with important functional heart

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biomarkers, suggesting the potential for myocardial tissue characterization with the use of 3D ECV by cardiac CT. This trial is registered at www.ClinicalTrials.gov as NCT01160471.

1. Introduction

Diffuse myocardial fibrosis is a common end point of a variety of cardiac risk factors and conditions, including diabetes, hypertension, hypertrophy, and even aging.[1] Myocardial extracellular volume fraction (ECV) is increased when fibrosis is present and may be a useful noninvasive marker of fibrosis.[2,3] The utility of ECV has been studied by gadolinium-enhanced cardiac magnetic resonance (MR) and involved blood pool and myocardial relaxivity before and after gadolinium quantitative T1 mapping.[2,4–6]

Cardiac CT has been validated for detection of focal myocardial scar[7–9] and myocardial perfusion.[10,11] Quantitative cardiac CT may similarly be used to map the iodine distribution in the myocardium. We have previously explored derivation of myocardial ECV on cardiac CT as a marker of interstitial fibrosis with the use of a 2-dimensional (2D) slice by slice approach,[12] showing good correlation with magnetic resonance imaging (MRI) results. That CT approach involved manual segmentation of only the lateral wall of the left ventricle on a single slice or few slices, because of difficulty in identifying blood pool versus ventricle on noncontrast CT.

We have developed a computational framework for ECV estimation[13] on CT consisting of the following 3 steps: (1) myocardium segmentation according to shape-constrained graph cut (GC) method, (2) cardiac image registration before and after contrast according to a symmetric Demons algorithm, and (3) ECV value computation. This method was tested, and the preliminary results showed the feasibility and efficiency of the proposed method. However, image processing/registration of CT before and after contrast remains an obstacle because of the need for operator intervention and long processing times.

Cardiac CT data are inherently 3 dimensional, and a 3-dimensional (3D) approach to whole-heart ECV derivation would likely improve ECV estimates. Further, whole-heart methods are generally not available for cardiac MRI. In this study, we present our results for the development of a 3D ECV calculation toolkit (ECVTK) to facilitate myocardium segmentation, CT registration before and after contrast, model generation, ECV calculation, and visualization. Our experiments indicate that ECVTK was more effective in improving the CT accuracy in comparison with our previous GC method.[13,14] Thus, this may produce a more efficient and user-friendly method for 3D ECV calculations. The purpose of this study was to develop and evaluate a 3D approach to determine ECV with the use of cardiac CT.

2. Methods

2.1. Study population

This study was approved by our institutional review board. All study participants provided written informed consent and completed both cardiac CT and cardiac MR studies at the same day within a 4-hour time window. From August 2010 to April 2012, 40 participants were enrolled. Patients with heart failure according to the New York Heart Association classification II or greater and either (1) left ventricular ejection fraction (LVEF) <40% or (2) evidence of elevated LV diastolic filling pressure and LVEF >50% were included as well as healthy persons for comparison, thus providing a wide range of ECV values. Healthy volunteers had no history of clinical cardiovascular disease, including myocardial infarction, heart failure, coronary artery disease, sudden cardiac death, or valvular heart disease.

Normal LV and right ventricular volumes and systolic functions were confirmed by cardiac MR as part of the routine study. Steady-state free-precession cine-MR short-axis images were acquired with temporal resolution of 40 milliseconds to assess LV function. Fast gradient echo images with the use of spatial modulation of magnetization (tagged MRI) was obtained for strain analysis.[15] Phase sensitive inversion recovery late gadolinium enhancement imaging was obtained at 15 minutes after injection to assess for focal myocardial scar. Inversion times were individually adjusted to suppress normal myocardium.[16]

Subjects with contraindications to cardiac MR or cardiac CT, including contrast reaction and glomerular filtration rate <30 mL/min/1.73m^2 were excluded. All clinical examinations and laboratory tests presented were evaluated no more than 7 days before the cardiac CT study.

2.2. Cardiac CT protocol

All study participants were imaged on a 320-multidetector CT scanner (Aquilion One; Toshiba Medical Systems, Tustin, CA, USA) after the cardiac MR examination. A calcium score type acquisition before contrast was performed with the use of prospective electrocardiogram (ECG) gating with a 400-millisecond single gantry rotation during inspiration breath hold that allows image acquisition at a single cardiac phase. Scan parameters were tube voltage of 120 kV, tube current of 300 mA, and slice thickness of 0.5 mm (reconstructed for 3 mm).[17] Coronary CT angiography was performed during intravenous infusion of 133 ± 16 mL of iopamidol (Isovue-370; Bracco Diagnostics, Plainsboro, NJ, USA) at a rate of 4–5 mL/s with the use of the following parameters: for heart rate <66 beats/min, prospective ECG gating at 70%–80% of 1 R–R interval, x-ray exposure time ranges from 0.423 to 0.350 second. For heart rate ≥66 beats/min, prospective ECG gating at 40%–80% of 2 R–R intervals, x-ray exposure time ranges from 1.174 seconds to 0.714 second. Additional parameters were tube voltage of 120 kV; tube current of 300–580 mA, depending on body mass index (BMI; calculated as weight in kg/height in m^2) and sex; gantry rotation speed of 0.35 second; slice thickness of 0.5 mm; and scan range of 128–160 mm.