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Extracellular volume quantitation using Dual-energy CT in patients with heart failure:

comparison with 3T cardiac MR

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Abstract

Backgrounds: Cardiac magnetic resonance (CMR) T1 mapping and the extracellular volume (ECV) have been developed to quantitative analysis of diffusely abnormal myocardial fibrosis (MF). However, dual-energy CT (DECT) has a potential for calculation of ECV. The aim of this study is to evaluate the feasibility and accuracy of DECT technique in determining the ECV in patients with heart failure, with 3T CMR as the reference.

Methods: Thirty-five patients with various reasons of heart failure were enrolled in this study. Both DECT and CMR exams were completed within 24 hours. ECVs were calculated, and the relationship between DECT-ECV, CMR-ECV, and other heart function parameters, including left ventricular end systolic and diastolic volume, cardiac output and ejection fraction (LVESV, LVEDV, CO, LVEF), Brain natriuretic peptide BNP) was determined. All participants gave informed consent, and the study was approved by the institutional review board.

Results: The median ECVs on DECT and CMR were 33% (95%CI: 32%-36%) and 30% (95%CI: 30% - 32%), respectively. A good correlation between myocardial ECV at DECT
and that at CMR (r=0.945, p<0.001) was observed. Bland-Altman analysis between DECT and CMR showed a small bias (2.6 %), with 95% limits of agreement of -0.4% and 5.6%.

Interobserver agreement for ECV at DECT was excellent (ICC = 0.907). Both ECVs, for DECT and CMR, were inversely associated with LVEF and CO.

**Conclusion:** DECT-based ECV could be an alternative non-invasive imaging tool for myocardial tissue characterization. However, overestimation of the extent of diffuse MF is observed with use of DECT.

**Key words:** heart failure; diffuse myocardial fibrosis; dual-energy CT; cardiac MR; extracellular volume
1. Introduction

Myocardial fibrosis (MF) occurs in a wide variety of heart conditions including heart failure with reduced or preserved ejection fraction (EF), diabetic and hypertensive heart disease, and non-ischemia cardiomyopathies. MF may represent a principal phenotype of cardiac vulnerability that improves risk stratification. Moreover, MF quantification is associated with cardiac outcomes [1, 2]. Endomyocardial biopsy is widely recognized as the “gold standard” for diagnosis of MF. However, its application is limited in the routine clinical practice given its intrinsic issues, such as invasive and serious complications. Recently, T1 mapping using cardiac magnetic resonance (CMR) imaging has been established as a reliable technique to quantify diffuse MF [2, 3]. CMR-derived extracellular volume fraction (ECV) calculated from native and contrast T1 maps, enables assessment of the extent of diffuse myocardial fibrosis [2]. CMR-derived ECV using T1 mapping has been validated in animal and human studies [4-6], including in patients with heart failure secondary to non-ischemic and ischemic cardiomyopathies, valve disease, cardiac amyloidosis and hypertrophic cardiomyopathy. However, CMR exam is not widely available and has some known contraindications. A recent published study showed that 5775 (16.7%) out of 34587 patients had failed MR exams because of unanticipated issue [7]. Moreover, the calculated ECV value is influenced by MR field strength, which is well documented that ECV value calculated from 3T MR are substantially different from that of 1.5 T MR[8].
Cardiac computed tomography (CCT) has been widely used in the clinical work-up of cardiac patients and can accurately measure myocardial perfusion [9, 10] and focal myocardial scarring [11]. In recent human studies [12, 13], CCT-derived ECV has demonstrated the ability to detect diffuse MF, with higher inter- and intra-observer reproducibility [14]. Although CCT has higher temporal and spatial resolution than CMR, it is less sensitive than CMR in terms of contrast resolution. Advanced dual source dual-energy CT (DECT) offers the possibility of tissue characterization using 2 different kV levels. DECT has been shown the potential for measuring ECV in both animal and humans studies [15, 16]. However, it is unclear that whether DECT could measure diffuse MF in heart failure patients. Therefore, the aim of this study is to evaluate the feasibility and accuracy of DECT derived -ECV for the assessment of diffuse MF in heart failure patients, compared with 3T CMR derived ECV, which is regarded as the reference method.
2. Methods

2.1 Study population

This was a single-center study approved by the local institutional review board. All participants gave written informed consent and completed both the DECT and CMR examinations within 24-hours. From December 2016 to October 2017, 35 patients with clinically diagnosed HF were prospectively enrolled in this study. The included heart failure patients were those with New York Heart Association (NYHA) grade II or higher, in addition to left ventricular ejection fraction (LVEF) <35% or HF with persistent LVEF >50%. Hematocrit and blood BNP measurements were performed within a 24-hour interval of the DECT and CMR exams. Exclusive criteria included: allergy to iodine; renal failure (glomerular filtration rate, GFR < 60 mL/min); pregnancy; patients with stent or CABG (coronary artery bypass graft).

2.2 DECT scan protocol and DECT-ECV analysis

All patients were examined with a second generation dual-source CT (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany). The CCT exam protocol included a prospective ECG-gated calcium score acquisition, a prospective ECG-gated coronary CT angiography (CCTA), and a delay DECT scan. The DECT scan was run after a 7-minute delay. For the prospective ECG-gated CCTA, the tube potential was selected based on the patient’s body mass index (BMI) and the tube current was modulated by automatic exposure control. The setting for patients with a BMI <24 kg/m² were 100 kV, and the setting for patients with a BMI ≥ 24 kg/m² were 120 kV. Bolus-tracking was
performed with a region of interest (ROI) placed in the root of the aorta, and image acquisition was automatically started 6 s after a predefined threshold of 100 HU was reached. The scanning range was set from the tracheal bifurcation to the diaphragm. Delayed post-contrast DECT was obtained with the following scan parameters: 185 effective mA at 100 kV, and 157 effective mA at 140 kV with a Sn filter, 64 ×0.6 mm collimation, 0.32 pitch factor, and 0.28 s rotation time. The effective radiation dose of CT was calculated by multiplying the dose-length product by a conversion factor of 0.014 [17].

The contrast agent was injected with a dual-head power injector (Stellant D, Medrad, Indianola, PA, USA) through an 18 G intravenous needle placed in the right antecubital vein. Depending on the scan time, 60-90 ml of contrast agent (Ultravist, 370 mg iodine/ml, Bayer, Wayne, NJ, USA) was injected, followed by 30 ml of saline as a bolus chaser. The injection rate was 4.5-5 ml/s for all phases.

2.3 Dual-energy CT data post processing

DECT post-processing was performed on a commercially available workstation (Syngo MMWP; Siemens Medical Solutions, Forchheim, Germany) using dedicated “Heart PBV (perfused blood volume)” software. First, DECT data was loaded into the Heart PBV. The software constructs iodine maps based on the material decomposition method, showing the distribution of iodine in the entire left ventricle myocardium. All iodine maps were reconstructed in short axis view from base to apex of heart with 8 mm slice thickness without any gap.
2.4 Dual-energy CT ECV measurement

Two observers selected iodine map images that matched the CMR T1 mapping images and measured independently. Overlay attenuation values of the myocardium and blood pool were obtained from the iodine maps. Depending on the 16-segment of LV myocardium (excluding 17th apex segment), ROIs were drawn manually in each segment in a conservative manner to avoid the periphery of the myocardium. At the same slice, a manual ROI with a minimum size of 100 mm² was drawn in the LV blood pool and papillary muscles were avoided (Fig 1). The DECT-ECV was calculated as follows:

$$ECV_{DECT} = \frac{HU_m}{HU_b} \times (1 - \text{hematocrit level}) \times 100\%,$$

where $HU_m$ is the attenuation value (Overlay value) of the myocardium (in Hounsfield units) and $HU_b$ is the attenuation value (Overlay value) of blood (in Hounsfield units) [15, 16].

2.5 Cardiac MR Protocol and CMR-ECV analysis

All CMR exams were performed on a 3T MR scanner (Verio; Siemens, Erlangen, Germany) with a 32-channel cardiovascular array coil (Vivo, Orlando, Fla). An 11-heartbeat modified Look Locker sequence with inversion recovery (MOLLI) was used for cardiac MR imaging T1 measurement, as described previously [2,3]. Scanning parameters were as follows: repetition time msec/echo time msec/minimum inversion time msec, 1.9/1.0/110.0; inversion time increment, 80.0 msec; field of view, 290 – 360 mm²; pixel size, 1.7 × 1.4 mm²; readout resolution, 192; phase resolution, 75% – 85%; section thickness, 8 mm; 35° flip angle; and generalized auto calibrating partially
parallel acquisition factor, 2. Short-axis images were acquired at the basal, mid-ventricle, and apical level of the LV.

Images for T1 measurements were obtained pre- and post- intravenous infusion of GA-DTPA (0.2 mmol/Kg, Magnevist; Bayer Healthcare Pharmaceuticals, Wayne, NJ) injected as a bolus at a rate of 0.15-0.2mL/sec/kg and followed by a 20-mL saline flush. Post-contrast examinations were performed at the same positions as pre-contrast examinations 15-20 minutes after the injection of contrast agent. Steady state free precession cine MR short-axis images were acquired for assessment of left ventricular function parameters (LVESV, LVEDV, and LVEF). Late gadolinium enhanced (LGE) MR imaging was performed 10 minutes after injection to detect local MF.

All CMR images were transferred to a dedicated workstation for image analysis (Siemens). The ROIs were placed comparable with the DECT images on both pre-contrast and post-contrast T1-mapping images at each segment of LV. The T1 LV blood pool value was measured a circular ROI (100 mm2), excluding the papillary muscles (Figures 1). The ECV fraction was calculated as follows: ECV_{CMR} = \Delta T1M/ \Delta T1B*(1-HcT)*100\% [2,3], \Delta T1M= T1 post-contrast Myocardium -T1-pre-contrast Myocardium, \Delta T1B= T1 post-contrast Blood -T1-pre-contrast Blood.

2.6 Statistical analysis

All statistical analyses were performed using statistical software (Medcalc 15.8,). Continuous variables are described as median (95% CI for median) because of no normal distribution. Comparison of ECV between CMR and DECT was assessed using the
Wilcoxon test. The correlation and the agreements between DECT-ECV and CMR-ECV were described with the Pearson test and the Bland-Altman plots, respectively. The correlation between DECT-ECV and left ventricular function parameters using CMR and BNP was assessed using linear correlation. Interobserver agreement was tested by calculating the intraclass correlation coefficient (ICC). P < 0.05 is recognized as statistical difference.
3. Results

3.1 Study characteristics

All 35 patients completed the DECT and CMR studies without any complications. The mean age was 59 years (range 48 – 69 years), and 14 of the patients were females. The patient characteristics are summarized in Table1.

3.2 ECV: Dual-energy CT vs. CMR

A total of 560 segments from 105 ECV maps were obtained at base, mid and apical levels from the DECT images in 35 patients. Ultimately, 75 segments were excluded from 15 ECV maps because of step artifacts and, 82 segments were excluded from 25 ECV maps because of focal LGE on DECT, resulting in 403 segments from 65 ECV maps analysis. Regarding CMR data was available for 75 out of 105 ECV maps. Excluding 112 segments from 30 ECV maps because of focal LGE, a total of 448 segments from 75 ECV maps were analyzed.

3.3 Correlation DECT-derived ECV and CMR-derived ECV between LV function parameters and BNP

The median ECVs on DECT and CMR were 33% (95%CI: 32%-36%) and 30% (95%CI: 30% - 32%), respectively. DECT-derived ECV values were higher than that of CMR (33% vs. 30%, p=0.009). The Bland-Altman plots between CMR-derived ECV and DECT-derived ECV were presented in Figure 2. The Bland-Altman plot shows a small bias (2.6 %) toward higher ECV at DECT, with 95% limits of agreement of 5.6 % and -0.4%. The average radiation dose of DECT was 4.21 ± 1.05 mSv.
ECV values showed good correlation between the CMR and DECT determined ECV values \((r=0.945, \ p<0.001)\). Both ECVs were inversely associated with LVEF and CO and showed a poor correlation with blood BNP (Table2). The inter-observer agreement for DECT ECV showed excellent agreement with an ICC of 0.907.
4. Discussion

In this study, we assess the performance of ECV derived from DECT for quantifying the diffuse MF in heart failure patients. Our results demonstrated that DECT-ECV could provide a reliable and accurately quantitative assessment of diffuse MF with good inter-observer agreement.

Similar to CMR determined ECV, CT determined ECV quantification requires image acquisitions pre- and post-contrast to determine the iodine concentration equilibrium in the myocardium and blood pool. When contrast-agent concentration equilibrium is equal in both the myocardium and the blood pool, myocardial ECV can be calculated through the known volume of distribution in blood (1-hematocrit). In a previous study, the feasibility of single energy cardiac CT (SECT) was developed to determine myocardial ECV through pre- and post-contrast cardiac CT scans; and its accuracy has been demonstrated [13]. And a good correlation was also shown between myocardial ECV measured with SECT and with CMR (r = 0.73) and histology (r=0.71) [12]. However, SECT has its inherent limitation with mismatch between pre- and post-contrast scans. The reason being that the lower spatial resolution of cardiac CT creates difficulty in differentiating myocardium and blood pool on pre-contrast CT scan [13].

In DECT, images with two different kV and mA settings were acquired simultaneously and were used to separate iodine and soft tissue based on different materials attenuation profiles [18]. Subsequently, the iodine distribution equilibrium in myocardium and blood pool after contrast can be measured using the iodine map from
the delayed scan. This method avoids the mismatch error of drawing ROIs at different positions caused by the separate acquisition using SECT. Hong et al. [15] reported on the novel use of DECT to characterize myocardial tissue changes in an animal model of doxorubicin-induced cardiomyopathy. Based on the iodine maps of the myocardium and blood pool, their result showed that ECV calculating from DECT has excellent agreement with histological \( (r=0.925) \) and CMR determined ECV\( (r=0.888) \). However, DECT determined ECV was slightly overestimated compared to CMR determined ECV (average overestimation of 3%-6%). This overestimation is also shown in the results of the Nacif et al’s study [13]. This overestimation of DECT (33% DECT ECV vs. 30% CMR ECV) was also observed in our study with CMR ECV as a reference. A small bias (2.6%) toward higher ECV was detected for DECT (Fig 2). Possible explanations for this are as follows: first, the mean value from Overlay Iodine map images overstates the iodine concentration in both myocardium and blood pool, leading to elevated DECT ECV value; second, the inherent shortcoming of CT technique, such as lower soft tissue contrast resolution, can result in an overestimation.

Increased CMR ECV was associated with left ventricle remodeling [19]. In a study by Nacif et al., EDV and ESV were positively correlated with SECT derived ECV, while EF was inversely correlation [13]. Our study showed an inverse correlation between LVEF/CO and both ECVs, which is clearly understood. However, the correlation between LV remodeling markers (EDV, ESV), serum biomarker (BNP) and DECT-ECV was poor.
In SECT ECV studies, the time-delay was 10 minutes to 25 minutes after contrast injection [12, 13]. In a previous DECT study, the time delay was set at 12-minutes after iodine contrast agents injection[16]. In an animal study, the time-delay was set at 3, 7, 10, 15 and 20 min, revealing no significant changes in the DECT ECV results [15]. According to these results, the time-delay should not influence the calculated ECV values. Thus, combined with results from a previous study about detecting the local myocardial scars [5], the time-delay of DECT was chosen at 7 minutes delay time in our study.

Regarding the contrast injection, there are two different injection methods (one phase bolus injection and bolus followed infusion injection) in published SECT or DECT studies. The one phase bolus injection is a predominant method in current studies. However, contrast bolus followed infusion protocol was considered acceptable in Bandula et al study [12]. Until now, there are no documents to support which contrast injection methods is superior for calculating myocardial ECV. However, the main shortcoming of last injection method was using relatively big volume of iodine contrast (143.2 ± 22.7 mL).

Another issue of concern is the radiation dose using DECT. In this study, the average radiation dose was 4.21 mSv, which is higher than both the pre- and post-contrast SECT acquisition protocol radiation dose (average 1.98 mSv) when using the retrospective ECG-gating protocol. A prospective ECG-gating protocol for DECT acquisition is available, which promises to significantly reduce the radiation exposure. However, in our pre-test data, the step artifacts were clearly present through the long-
axis, short-axis and four-chamber views of the LV, which seriously undermines the image quality and decreases the accuracy of the DECT ECV measurements.

5. Study limitations

This study has several limitations. First, this is a single center prospective study. A lack of normal ECV value, measured in healthy volunteers is rarely available in both DECT and CMR exam at the relatively short time interval. Second, the HCT value influences the calculation of ECV in both of DECT and CMR. Collecting HCT twice at different examination days was not possible for each patient. Therefore, it was aimed to perform both DECT and CMR on the same day. Third, this study included relatively small volume of patient population. The results should therefore be validated in a larger cohort.

6. Conclusion

In summary, the findings of this study confirm that DECT derived ECV provides a good agreement of measurement in diffuse MF to CMR imaging, although DECT may slightly overestimate the ECV value. Given the increasing importance of cardiac CT, this work is exciting in its potential to provide a much more efficient, accurate, and widely available noninvasive measure of myocardial tissue characteristics, especially in patient with contraindications to CMR.
Acknowledgement

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References


Figure 1

Iodine map shows measurement of myocardial ECV with overlay attenuation values (in Hounsfield units). In this patient, a 63-year-old woman with HF, the overlay attenuation value is 25 HU for the anterior wall, 25.8 HU for the anteroseptal wall, 27.5 HU for the inferior-septal wall, 32.4 HU for the inferior wall, 27.2 HU for the inferior-lateral wall and 29.6 HU for the lateral wall of the mid left ventricle. The overlay attenuation value for blood is 47.1 HU, and the serum hematocrit level of the patient is 37.8%. From these values, the myocardial ECV is calculated as 31.83% for the anterior wall and 44.88% for the anteroseptal wall of the mid left ventricle. On MR images, the myocardial ECV is 32.46% for the anterior wall and 43.12% for the anteroseptal wall.

Figure 2

Bland-Altman plot shows a small bias (2.6%) toward higher ECV at DECT (black line), with 95% limits of agreement between the two methods of 5.6% and -0.4% (thick gray lines).
Table 1: Basic characteristics of participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tr>
<td>Age</td>
<td>59 years</td>
</tr>
<tr>
<td>Gender</td>
<td>21 male, 14 female</td>
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<tr>
<td>Body mass index (BMI)</td>
<td>25.30 ± 2.14</td>
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<tr>
<td>Ischemia cardiomyopathies</td>
<td>9 (26%)</td>
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<td>Dilated cardiomyopathies</td>
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<td>Hypertensive heart disease</td>
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<tr>
<td>Noncompaction of left ventricular myocardium</td>
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<tr>
<td>Heart failure with New York Heart Association (NYHA)</td>
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<tr>
<td>NYHA I</td>
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<tr>
<td>NYHA II</td>
<td>16 (46%)</td>
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<tr>
<td>NYHA III</td>
<td>14 (40%)</td>
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<tr>
<td>NYHA IV</td>
<td>5 (14%)</td>
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<td>Hematocrit level (%)</td>
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<td>BNP</td>
<td>1687 ± 1449</td>
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<td>Cardiac function parameters</td>
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<tr>
<td>LVEF (%)</td>
<td>18 ± 9.51</td>
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<tr>
<td>LVEDV (ml)</td>
<td>220 ± 78</td>
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<tr>
<td></td>
<td></td>
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<td>----------------------</td>
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</tr>
<tr>
<td>LVESV (ml)</td>
<td>186 ± 82</td>
</tr>
<tr>
<td>LV CO (ml/kg/min)</td>
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<tr>
<td>DECT effective radiation dose (mSv)</td>
<td>4.21 ± 1.05</td>
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<td>R value at DECT-ECV</td>
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Highlights

1. Higher ECV occurred in heart failure patients

2. DECT could be an alternatively, reliably non-invasive imaging tool for myocardial tissue characterization

3. Both ECVs, for DECT and CMR, were inversely associated with LV EF and cardiac output
Figure 1
Figure 2