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Computed tomography-derived myocardial extracellular volume fraction — a redundant by-product or a novel promising marker?

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Abstract: Myocardial extracellular volume (ECV) expansion is associated with myocardial abnormalities such as interstitial fibrosis, inflammation or amyloid deposition. Our aim was to search for correlates of ECV fraction (ECVF) derived from routine cardiac computed tomography (CT) of real-world patients. We retrospectively calculated ECVF from archived chest CT scans performed in 103 patients (51 women and 52 men; mean age: 66 ± 13 years) during a diagnostic work-up based on clinical indications. From recorded echocardiographic images, we calculated indices of left ventricular (LV) structure and function, including systolic (S') and diastolic (E' and A') mitral annular velocities. There were no significant relations between ECVF and clinical or echocardiographic parameters. LV function was comparable according to median ECVF (24.7%) (S': 10.4 ± 4.1 vs. 9.5 ± 8.0 cm/s; E': 9.2 ± 3.4 vs. 9.4 ± 3.1 cm/s; E'/A' ratio: 1.0 ± 0.6 vs. 1.2 ± 0.9; E/E' ratio: 9.0 ± 4.8 vs. 9.4 ± 5.8 for ECVF above and below the median, respectively). S' and E' were positively correlated in 52 subjects with an over-median ECVF ($r = 0.46$, $p = 0.001$), in contrast to their 51 counterparts with a below-median ECVF ($r = 0.15$, $p = 0.3$). In conclusion, ECV expansion might be associated with a marked interdependence of S' and E', corresponding to systolic and early diastolic LV performance, respectively. As E' is a rough surrogate index of LV active relaxation, these findings could reflect a contribution of LV fibrosis to early LV diastolic dysfunction, known to coincide with discrete LV long-axis systolic dysfunction. Further studies are warranted to investigate relations between CT-derived ECVF and LV mechanics.

Keywords: myocardial fibrosis, left ventricular function, computed tomography.

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Introduction

Assessment of extracellular volume (ECV) using magnetic resonance (MR) imaging is increasingly gaining importance as a valuable tool to evaluate myocardial abnormalities and support diagnosis [1]. ECV fraction (ECVF) corresponds to the percentage of the myocardium composed of elements other than cardiomyocytes. Normal ECVF ranges 20–30% in individuals without cardiovascular diseases [2, 3]. Elevated ECVF accompanies various cardiac pathologies involving myocardial fibrosis [4]. It has been demonstrated that fibrosis is virtually always present in late stages of heart failure, being an independent prognostic factor for adverse cardiovascular events [5, 6]. Furthermore, ECV assessment appears useful in patients with myocarditis, amyloidosis and dilated cardiomyopathy [3].

ECVF is mostly calculated from MR images with T1 mapping [7], which can be technically demanding and costly. A limited access to MR has spurred interest in assessing ECVF using CT imaging. Bandula *et al.* [8] proposed a feasible method to compute ECVF from contrast and non-contrast CT images. Recent studies have shown a close correlation between CT-derived and MR-derived ECVF [9, 10]. However, a marked contribution of CT-protocol parameters to the heterogeneity in CT-ECVF estimates was also reported [11]. Accordingly, the assessment of ECVF by CT might be a reliable approach with a potential for clinical use.

Our aim was to search for clinical and echocardiographic correlates of ECVF derived from routine cardiac CT scans of real-world patients.

Materials and Methods

Study population

We retrospectively analyzed medical records of 103 patients (51 women and 52 men; mean age: 66 ± 13 years) hospitalized in the University Hospital in Cracow who had both echocardiographic and CT examinations performed within a one-year interval. The protocol, including a retrospective analysis of both medical histories and recorded ultrasound and CT images, was approved by the Research Ethics Committee of the Jagiellonian University Medical College (Approval number: 118.0043.1.353.2024 of October 25th, 2024).

Analysis of CT scans

CT images were obtained in all study subjects using University Hospital of Cracow database of archived chest CT-scans. Analysis of all CT-scans was conducted using SyngoVia software. The objective of analyzing acquired CT images was to determine the mean ECVF within the interventricular septum. To achieve this, the investigator conducting the image analysis relied on the evaluation of arterial, delayed and native phase images of archive CT-scans. Firstly, the exact location of structures within myocardium was determined using arterial phase images. These images served as a guidance tool to determine CT-slices which depicted interventricular septum in a manner that enabled further measurements. In those slices, where myocardial structures were best visualized, a region of interest (ROI) with an circular area of 25 mm^2 (app. 5.64 mm in diameter) was determined. This demarcated area was transferred to both native and delayed phase images to ensure that the regions identified in each phase reflected the same myocardial

area and consisted only of the myocardium, excluding the endocardium. The following step involved measuring attenuation in native and delayed phase images at the ROI and displaying those results in Hounsfield units (HU).

An analogous process was performed to obtain the attenuation index of blood, which required placing a second circular ROI of 130 mm^2 (approximately 12.87 mm in diameter) in the ventricular lumen to identify an area containing only blood avoiding papillary muscles. Both measurements were taken in the exact same time-frame which ensured comparability of obtained results. The sizes and geometry of the analyzed ROIs were determined based on similar studies available in the literature. The procedure resulted in obtaining four independent indices (expressed in Hounsfield units [HU]): post-contrast myocardial attenuation [A], native myocardial attenuation [B], post-contrast attenuation of blood [C] and native attenuation of blood [D].

Obtained values were substituted into the special formula provided by Bandula *et al.* [8]:

$$ECVF = (1 - \text{hematocrit}) \times [(A - B) / (C - D)],$$

which allowed to determine an estimated ECVF value for each one of the patients. Hematocrit values were extracted from medical records under the condition that blood sampling and CT scan were performed within 48 hrs.

Analysis of echocardiographic images

Echocardiographic data were obtained from the database of archived echocardiographic images. All parameters were analyzed by the authors using the ViewPoint software to ensure a high quality. The parameters of LV structure and function included classical echocardiographic parameters and indices derived from tissue Doppler imaging, i.e. peak systolic velocity of the mitral annulus (S'), peak early diastolic (E') and late (A') velocities of the mitral annulus, as well as E'/A' ratio and E/E' ratio, i.e. the ratio of peak early transmitral blood flow (E) to E', an index of LV filling pressure.

Statistical analysis

Data are shown as means ± standard deviations (SD) or numbers (n) and percentages. The concordance with a normal distribution was verified by Kolmogorov–Smirnov test. Intergroup comparisons of ECVF were performed by Student's t-test of Fisher's exact test for continuous and categorical data, respectively. Bivariate correlations were estimated by Spearman's correlation coefficients (r). The statistical significance was inferred at a p-value below 0.05.

Results

The study group included 51 women and 52 men (mean age: 66 ± 13 years), out of whom 59 and 24 had coexistent hypertension and type 2 diabetes, respectively. Mean ECVF was 25.2 ± 8.8%, exhibiting a Gaussian distribution.

There were no significant differences between 52 patients with an over-median ECVF compared to their 51 counterparts with a below-median ECVF in any echocardiographic (Table 1) or clinical characteristics (Table 2).

Table 1. Echocardiographic characteristics according to median ECVF.

Characteristic	ECVF [%]		p
	≥24.7 n = 52	<24.7 n = 51	
LVIDd (cm)	4.6 ± 0.7	4.9 ± 0.7	0.1
LVPWd (cm)	0.9 ± 0.2	1.0 ± 0.2	0.1
RWT	0.4 ± 0.12	0.43 ± 0.12	0.4
LA-width (cm)	4.1 ± 0.9	4.3 ± 0.9	0.3
S' (cm/s)	10.4 ± 4.1	9.5 ± 8.0	0.5
E (cm/s)	73.3 ± 21.1	74.5 ± 18.2	0.8
A (cm/s)	83.3 ± 26.7	79.8 ± 29.1	0.5
E/A	1.0 ± 0.6	1.1 ±0.6	0.4
E' (cm/s)	9.2 ± 3.4	9.4 ± 3.1	0.7
E'/A'	1.0 ± 0.6	1.2 ± 0.9	0.3
E/E'	9.0 ± 4.8	9.4 ± 5.8	0.7

Data are shown as mean ± SD. ECVF: extracellular volume fraction; A: peak late transmitral flow velocity; A': peak late diastolic velocity of the mitral annulus; E: peak early transmitral flow velocity; E': peak early diastolic velocity of the mitral annulus; LA: left atrium; LVIDd: left ventricular (LV) internal dimension at end-diastole; LVPWd: LV posterior wall thickness at end-diastole; RWT: relative LV wall thickness; S': peak systolic velocity of the mitral annulus.

Table 2. Clinical characteristics according to median ECVF.

Characteristic	ECVF [%]		p
	≥24.7 n = 52	<24.7 n = 51	
Age (years)	65 ± 12	66 ± 14	0.7
Women (n, %)	27 (52%)	24 (47%)	0.7
Body-mass index (kg/m^2)	25.9 ± 5.4	27.2 ± 5.4	0.3
eGFR (ml/min per 1.73 m^2)	68 ± 23	70 ± 25	0.7
Diabetes (n, %)	10 (19%)	14 (27%)	0.4
Hypertension (n, %)	31 (59%)	28 (55%)	0.9
A history of myocardial infarction	9 (17%)	9 (18%)	>0.9

Data are shown as mean ± SD or n (%). eGFR: estimated glomerular filtration rate by the CKD-EPI formula.

In particular, S' was 10.4 ± 4.1 cm/s in the above-median group compared to 9.5 ± 8.0 cm/s in the below-median group (p = 0.5), and E' averaged 9.2 ± 3.4 cm/s and 9.4 ± 3.1 cm/s in the respective groups (p = 0.7). The E/E' ratio (an index of LV filling pressure) was 9.0 ± 4.8 in the patients with an ECVF over the median and 9.4 ± 5.8 in those with an ECVF below the median (p = 0.7) (Table 1).

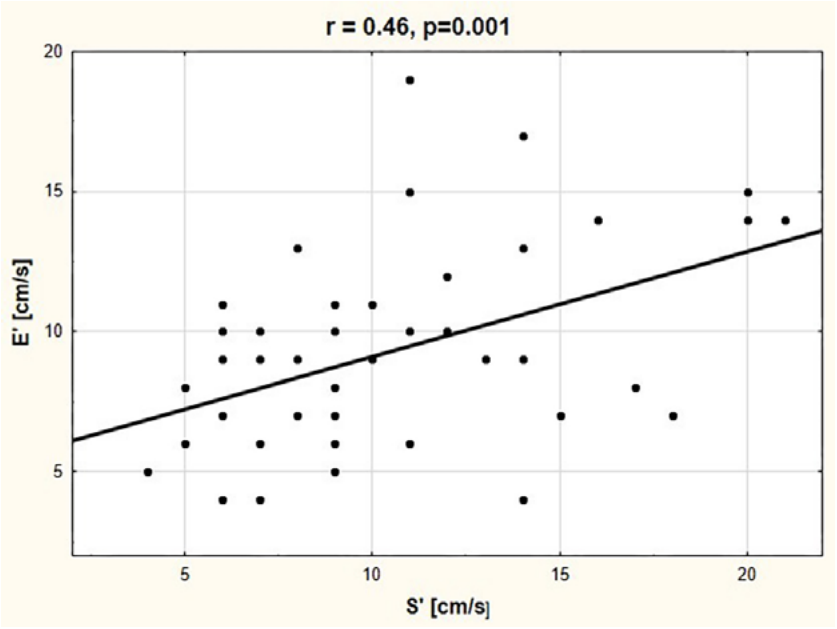

Fig. 1. A positive correlation between peak systolic (S') and peak early diastolic (E') velocity of the mitral annulus in patients with an extracellular volume fraction over the median (≥24.7%).

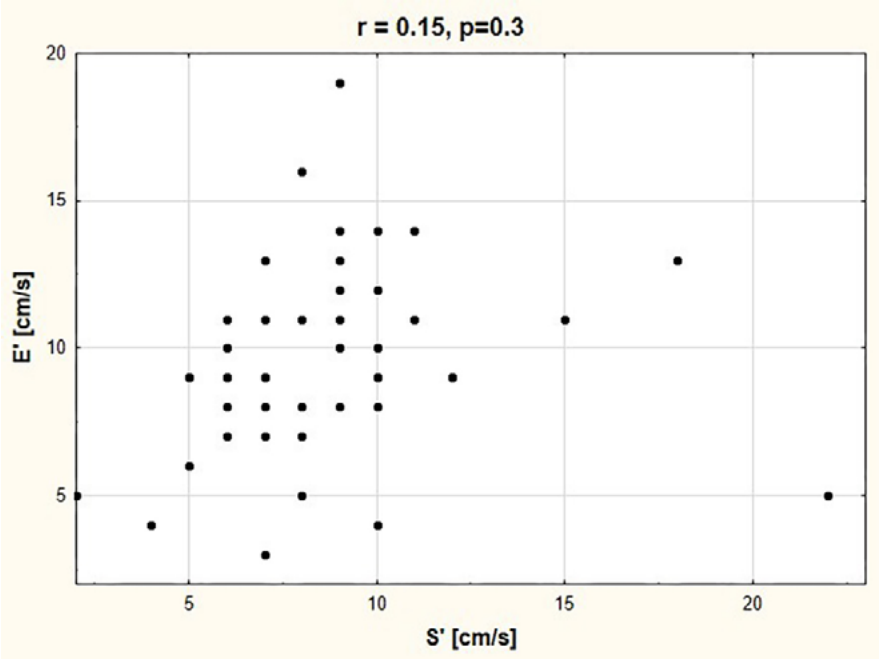

Fig. 2. No correlation between peak systolic (S') and peak early diastolic (E') velocity of the mitral annulus in patients with an extracellular volume fraction below the median (<24.7%).

Interestingly, a positive correlation between S' and E' was identified in the subgroup of 52 subjects with an ECVF above the median ($r = 0.46$, $p = 0.001$) (Fig. 1). This correlation was not observed in the 51 subjects with an ECVF below the median, where the relationship between S' and E' was not statistically significant ($r = 0.15$, $p = 0.3$) (Fig. 2).

Discussion

Our preliminary results suggest that ECV expansion may be linked to a mutual interdependence of E' and S', markers of early diastolic and systolic LV performance, respectively. Since E' reflects LV active relaxation [12], these findings may indicate a contribution of LV fibrosis to an early stage of LV diastolic dysfunction, also associated with discrete LV long-axis dysfunction, which may in turn further impair early diastolic function via depressed elastic restoring forces.

Several studies have consistently reported no close associations between ECVF and LV function or traditional cardiovascular risk factors [11, 13–15]. It was demonstrated that only amyloidosis was associated with a substantial increase in ECVF, whereas diastolic heart failure, systolic heart failure, diabetes, hypertension and obesity coexisted with only slight, if any, ECVF elevations [13–16]. This could be a plausible explanation of the lack of relationship between ECVF and any clinical or echocardiographic parameters in the present report.

That classical cardiovascular risk factors are at best only weak predictors of ECVF, is also consistent with the results of a study by Wong *et al.* [13] who compared ECVF values between individuals with and without diabetes. In that study [13], 231 diabetic patients had significantly higher median ECVF than 945 subjects without diabetes, nonetheless, the effect of diabetes was relatively mild (about 7%). Accordingly, since the number of our study patients was low, the present study design had no sufficient ability to detect such subtle differences.

In an extension of these observations, Su *et al.* [15] found no significant correlations between myocardial ECVF and LV ejection fraction, end-diastolic volume, end-systolic volume, peak ejection rate and peak filling rate, regardless of the presence of heart failure. This suggests that myocardial ECVF, a marker of diffuse myocardial fibrosis, is unable to directly affect these parameters. Similarly, Treibel *et al.* [16] reported only insignificantly higher ECVF in hypertensive patients compared to healthy individuals, except for small but statistically significant ECVF rises in those with hypertension and coexistent LV hypertrophy. Nevertheless, ECVF and echocardiographic indices of LV diastolic function were mutually unrelated in that study [16], which further supports our findings.

Conclusions

Our preliminary findings could reflect a contribution of LV fibrosis to an early stage of LV diastolic dysfunction, known to coincide with discrete LV long-axis systolic dysfunction. Further large-scale studies are warranted to investigate relations between CT-derived ECVF and LV mechanics.

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