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**Distribution of left ventricular trabeculation across age and gender in a cohort of 140
healthy Caucasian subjects**

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Abstract

Rationale and objectives

This study sought to quantify the distribution of trabeculated (T) and compact (C) left ventricular (LV) myocardium masses in a healthy Caucasian population against age, gender and LV parameters, and to provide normal values for T, C and T/C.

Materials and methods

One hundred and forty healthy subjects were prospectively recruited and underwent cardiac MRI at 1.5T with a stack of short-axis cine sequences covering the entire LV. End-diastolic volume (EDV), C and T masses were quantified using a semiautomatic method. Ejection fraction (EF) and T/C ratio were computed.

Results

We included 70f/70m, mean age: 44 years \pm 14, range: [20-69]. The mean EF was 63.7 \pm 6.3%[50.7-82.0], the mean EDV was 75.9 \pm 16.2ml/m²[36.4-112.2], the mean C mass was 53.9 \pm 11.2g/m²[26.5-93.4] and the mean T mass was 4.9 \pm 2.4g/m²[1.1-11.4]. The T/C ratio was 9.2 \pm 4.5%[2.0-29.4]. Multivariate ANOVA test showed that the compact mass was influenced by EDV (P <0.0001), EF (P =0.001) and gender (P <0.0001), and the trabeculated mass depended on EDV (P <0.0001), gender (P =0.002) and age (P <0.0001), while the T/C ratio was only impacted by age (P =0.0003). Spearman test showed a correlation between EDV and C (r =0.60, P <0.0001), T (r =0.46, P <0.0001) and T/C ratio (r =0.26, P =0.0023). Only T and T/C ratio were correlated to EF (r =-0.18, P =0.0373; r =-0.18, P =0.0321 respectively).

Conclusion

While the compact and trabeculated myocardium masses appear to relate separately to the cardiac function, age and gender, their ratio T/C appears to only decrease with age.

Furthermore, we propose here normal values for T, C and T/C in a cohort of healthy Caucasians subjects.

Running title: Distribution of LV trabeculations in healthy Caucasian subjects.

Key words

Myocardium; Left Ventricular Remodeling; Isolated Noncompaction of the Ventricular Myocardium; Left Ventricular Function; Healthy Volunteers.

Abbreviations and acronyms

BSA: body surface area

bSSFP: balanced steady-state free precession

C: compact myocardium mass

CI: confidence interval

DCM: dilated cardiomyopathy

ECG: electrocardiogram

ED: end-diastolic

EDV: end-diastolic volume

EF: ejection fraction

ES: end-systolic

FOV: field of view

HCM: hypertrophic cardiomyopathy

ICC: intraclass correlation coefficient

LV: left ventricle

LVNC: left ventricular non-compaction

MRI : magnetic resonance imaging

SD: standard deviation

T: trabeculated myocardium mass

Introduction

Cardiac MRI has emerged as a reference modality for heart diseases investigation. It's a valuable non-invasive tool allowing an accurate morphological and functional characterization of the heart in several clinical conditions[1,2].

Excess of trabeculation is a trait shared by several cardiomyopathies such as left ventricular non compaction (LVNC) [3]or hypertrophic cardiomyopathy (HCM) [4]. Excess of trabeculation was also described in pregnant women [5] or highly trained athlete [6]. Trabeculations are normal constituent of the left ventricle (LV) endocardial layer and discriminating between normal and excess of trabeculation is still a matter of debate.

Therefore, there is a need for reliable quantification of trabeculations in the LV myocardium and its variations in a healthy population. Indeed, to date, there is no criteria or method considered as gold–standard for differentiating between normal and pathological trabeculation of the myocardium. Recent semi-automatic method to quantify compact (C) and trabeculated (T) LV myocardium masses from cardiac magnetic resonance imaging (MRI) has been established and validated [7]. However, this method has yet to be evaluated in terms of the range of “normal” healthy values of LV masses in a large cohort.

The aim of this paper was to quantify the distribution of T and C myocardium masses across age and gender in a healthy population and to provide normal values for T, C and T/C ratio in healthy Caucasian subjects.

Materials and methods

Recruitment

This study was approved by the local Institutional Review Board in accordance with the guidelines outlined in the Declaration of Helsinki. One hundred and forty healthy volunteers were enrolled for a cardiac MRI examination after providing informed consent. Among them, forty-one were already included in an initial study by Bricq et al. [7]. An additional ninety-nine healthy subjects (clinical trial NCT01712581, clinicaltrials.gov) were prospectively recruited from October 2012 to June 2014 and included in this cohort. A pregnancy test was performed for all female participants of childbearing age. Inclusion criteria were: age over 18 and below 70 years old, ability to understand and sign the consent form, ability to maintain supine position for 20 minutes, no cardiac symptoms, normal cardiovascular examination results and no known risk factors or history of cardiac disease. Exclusion criteria were: claustrophobia, transfused subjects, haematological disease, iron deficiency, high blood pressure, contraindication for MRI, pregnancy, diabetes and arrhythmias.

Image acquisition

Magnetic resonance (MR) examinations were performed on a 1.5 T Avanto[®] scanner (Siemens Healthineers, Erlangen, Germany) using a multichannel body array coil combined with a spine array coil with the subjects in supine position. A stack of balanced steady-state free precession (bSSFP) cine sequences were acquired in short axis view in order to cover the whole LV from base to apex with a total of 7 to 14 slices. Acquisitions were electrocardiogram (ECG) synchronized and performed under inspiratory breath hold using the following typical parameters set: flip angle: 77°, pixel bandwidth: 930Hz, spatial resolution between 1.37x1.37mm² and 1.48x1.48mm², slice thickness: 6mm, gap between slices: 9mm,

repetition time: 3.62ms, echo time: 1.51ms, parallel imaging 2x (GRAPPA [8]). The resolution and the flip angle were adapted to subject morphology for each individual.

Image analysis

Argus[®] Ventricular Function software (Siemens Healthineers, Erlangen, Germany) was used to quantify end diastolic volume (EDV), end systolic volume (ESV), end diastolic LV mass and to compute the ejection fraction (EF) for all subjects. The end-diastolic (ED) image was defined as the frame with the largest blood pool volume in the LV cavity. The end-systolic (ES) image was determined as the frame with the smallest blood pool volume in the LV cavity. The most basal slice of the LV was defined as the slice showing at least 50 % of the LV myocardium circumference at ED. The most basal section could differ between ED and ES.

LV trabeculations, endocardial and epicardial borders were defined, in the whole stack of the diastolic phase, using the semi-automatic method proposed by Bricq et al. [7] (Fig1). Compact (C) and trabeculated (T) myocardium masses were defined as the difference between the epicardium and the endocardium and between the trabeculation contour and the endocardium respectively, as described in [7]. Papillary muscles were included in the compact LV myocardium mass. C and T masses were indexed to the body surface area (BSA) to take into account variation of height and weight between subjects. The T/C ratio was then computed and expressed as a percentage. All left ventricular parameters, C and T measurements were done by an operator (Op-1, three-year experience, Image Processing Engineer). A second operator (Op-2, two-year experience, Doctor) repeated the measurements on 10 randomly assigned subjects to evaluate inter-observer variability. To assess intra-observer variability, measurements were repeated by the first operator on 20 randomly selected subjects, at least 3 weeks later. All operators were blinded to the subject

characteristics (age and gender) and to the other operator measurements. A representation of T/C ratio mean values across age and gender was produced for the 16 LV segments.

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 7.0a (GraphPad software Inc., San Diego, CA). The intraclass correlation coefficient (ICC) and Bland-Altman method comparison were used to evaluate the reproducibility between two segmentations by Op-1 and between segmentations by Op-1 and Op-2. Values were reported as mean \pm standard deviation (SD). The mean values were calculated according to gender (70 males and 70 females) and age (5 groups of 28 subjects, 14 men and 14 women). BSA was calculated using the formula of Dubois and Dubois [9]. D'Agostino & Pearson normality test was performed for the 5 age groups and each gender. For each variable (EF, EDV, ESV, T, C and T/C ratio), a non-parametric analysis (Mann-Whitney test for genders, Kruskal-Wallis test and Dunn multiple comparisons post-hoc test for age groups) was used to compare groups who did not pass the normality test. Groups who passed the normality test were analysed using a parametric test (Welch's t test for genders, ordinary one-way ANOVA with Tukey's multiple comparisons test for age groups). A Multivariate ANOVA (MANOVA) was performed to test the influence of gender and age on quantitative cardiac MRI measurements. A Spearman test was also performed in order to measure the correlation between LV masses and the other LV parameters (EF and EDV). Significance was set to $P < 0.05$.

Results

Participant Characteristics

Volunteers (70 men and 70 women) were organised so as to include 14 men and 14 women in each of the 5 following groups: first group, age between 20-29 years old; second group, age between 30-39 years old; third group, age between 40-49 years old; fourth group, age between 50-59 years old and the fifth group, age between 60-69 years old. Subject characteristics were summarized in Table 1. All quantitative variables were expressed as mean±SD and ranges. There was no significant difference ($P>0.05$) between any age group in terms of height, weight and BSA. Men had significantly greater BSA than women ($P<0.0001$).

Left ventricular parameters

Regarding the ejection fraction (EF), all age groups were similar, but there was a significant difference ($P=0.0178$) between men ($62.4\pm 6.1\%$) and women ($64.9\pm 6.2\%$) as shown in Table 2. EF increased significantly with age ($P=0.0184$) (Fig. 2a). The mean value of end-diastolic volume (EDV) was significantly greater in men ($78.8\pm 18.0\text{ ml/m}^2$) than in women ($72.8\pm 13.6\text{ ml/m}^2$, $P=0.0280$). When comparing EDV across age groups, it decreased significantly with age from $87.13\pm 16.74\text{ ml/m}^2$ in the youngest to $67.37\pm 17.09\text{ ml/m}^2$ in the oldest ($P<0.0001$). ESV also decreased significantly with age ($P<0.0001$) (Fig. 2b) with significant difference between men and women ($P=0.0052$) and the age group 20-29 and 40-49 ($P=0.0005$), 50-59 ($P=0.0017$) and 60-69 ($P<0.0001$).

Left ventricular masses across gender and age groups

There was no significant difference between age groups in terms of compact myocardium mass. The mean value of C was significantly greater in men ($60.0\pm 9.1\text{ g/m}^2$) than in women ($47.7\pm 9.8\text{ g/m}^2$, $P<0.0001$) (Table 2). While on the other hand, C remained stable across age (Fig. 2c).

Trabeculated myocardium mass decreased significantly with age from $6.85 \pm 2.56 \text{ g/m}^2$ in the first age group 20-29 to $3.97 \pm 1.99 \text{ g/m}^2$ in the oldest (fifth age group: 60-69) ($P < 0.0001$) (Fig. 2c) with significant difference between the first group (age between 20-29) and all the other age groups (30-39, $P = 0.0072$; 40-49, $P = 0.0025$; 50-59, $P = 0.0001$; and 60-69, $P < 0.0001$). The difference was also significant between genders with greater values for men: $5.4 \pm 2.3 \text{ g/m}^2$, compared to women: $4.0 \pm 2.3 \text{ g/m}^2$ ($P = 0.0052$) (Table 2).

T/C ratios were not significantly different between genders ($9.1 \pm 3.7 \%$ for men and $9.2 \pm 5.2 \%$ for women). The T/C ratio was decreasing with age from $12.33 \pm 4.57 \%$ in the youngest to $7.55 \pm 3.49 \%$ in the oldest ($P = 0.0003$) (Fig. 2d). There was also a significant difference between the first age group 20-29 and the age groups 40-49 ($P = 0.0390$), 50-59 ($P = 0.0009$) and 60-69 ($P = 0.0006$).

Values of the T/C ratio for men and women in each age group are listed in Table 3, as mean \pm SD and 95% confidence interval (CI).

Observer variability

Mean and SD of T, C and T/C ratio for the intra-observer variability, are provided in Table 4. The ICC (Table 4, ICC) was high (> 0.90) for all parameters (T, C and T/C ratio). The Bland-Altman bias between the segmentations was $-0.16 \pm 0.39 \text{ g}$ for T mass, $0.70 \pm 2.00 \text{ g}$ for C mass and $-0.21 \pm 0.47 \%$ for the T/C ratio.

Table 4 displays also the variability between the two experts Op-1 and Op-2 where the ICC was computed. We had a high ICC (≥ 0.80) for C, T and T/C ratio. Bland-Altman bias was found to be $-0.64 \pm 0.39 \text{ g}$ for the T mass, $-3.61 \pm 6.04 \text{ g}$ for the compact myocardium mass and $-0.58 \pm 1.81 \%$ for the T/C ratio. The mean values \pm SD for the three parameters (T, C, and T/C ratio) are also given in Table 4.

Relationship between LV masses and age, gender and LV parameters

In terms of trabeculated myocardium mass, there was a significant correlation with age, gender and EDV, but not with EF. The only factor independently linked with the T/C ratio variation was age (Table 5).

The Spearman test showed a positive correlation between EDV and C, T and T/C ratio ($r=0.60$, $P<0.0001$; $r=0.46$, $P<0.0001$; $r=0.26$, $P=0.0023$ respectively), but only T and T/C ratio were negatively correlated to EF ($r=-0.18$, $P=0.0373$; $r=-0.18$, $P=0.0321$ respectively).

Values of the T/C ratio across the 16 LV segments

The distribution of the highest T/C ratios (over 20 %) was found in apical anterior and apical lateral segments. T/C ratios in the basal third did not reach 10 % for any subject regardless of gender and age as shown in Fig. 3.

Discussion

The main findings of this study were: 1) Local distribution of trabeculations showed that T/C ratios vary substantially across the LV, with higher ratios in apical anterior and apical lateral segments. 2) The T/C ratio was inversely correlated with age and independent to LV volumetric parameters in that cohort.

Trabeculations are normal constituent of LV and discrimination between normal trabeculation and hypertrabeculation remains a matter of debate [10]. The presence of hypertrabeculation has been linked with a response to mechanical load which may disappear as the mechanical load dissipates [5,6]. Therefore, the evocation of hypertrabeculation might have important consequence in highly trained athletes. Furthermore, hypertrabeculation was diagnosed in asymptomatic subjects with normal or nearly normal ejection fraction [11]. Criteria based on segmental analysis using ultrasound (US), used to diagnose hypertrabeculation, are poorly correlated and are prone to confounding factors [12]. Kohli et al. showed that segmental measurements of T and C thickness using US are too sensitive to partial volume effect and slice selection. Authors concluded that those criteria result in over diagnosis of LVNC. Using MRI, Kawel et al. showed in 323 healthy subjects without cardiac disease or hypertension that more than 40% of subjects presented a trabeculated over compact myocardium thickness ratio higher than 2.3 [13]. However, the thickness ratio was assessed in only one segment in that study. The present study confirmed that LV trabeculations are not homogeneously distributed over LV cavity and a segmental measurement of trabeculation might reflect this variation. André et al. [14] showed similar result using MRI in 117 healthy subject using only the long axis view. Quantification of the total amount of LV trabeculation appears preferable to assess normal LV trabeculation and already showed ability to discriminate between normal and diseased patients [15]. Our results were in line with the current literature in which the T/C ratio varies from 9.7 to 12.0 % [15–17]. Papavassiliu et al.

found that trabeculae account for 10 % of the left ventricular mass [16], but only 20 healthy volunteers were included using a fast-gradient echo sequence, whereas bSSFP sequences with higher resolution would be beneficial [18]. Using a manual segmentation and bSSFP sequences, Jacquier et al. found a T/C ratio of 12 ± 5 % for healthy subjects [15]. Grothoff et al. assessed the T/C ratio by manual contouring in 24 healthy volunteers and found a mean value of 9.9 ± 4.4 % [17].

Obtaining normal values and ranges for trabeculated mass and T/C ratio is crucial as trabeculated myocardium is a determinant phenotypic expression in several cardiac diseases. In an early study, Kozor et al. showed that, in Fabry disease and in HCM, both relative papillary muscle mass and T mass values were increased [19]. In contrast, these authors also showed that neither in hypertrophy linked to afterload increase (aortic stenosis and hypertension) nor in amyloidosis were there increased trabeculations. Furthermore, Choudhary suggested that a higher T/C ratio was associated with a higher prevalence of electrical disturbances including sustained ventricular tachycardia in patients suffering from LVNC [20]. Therefore a precise quantification of LV trabeculation might be clinically relevant to discriminate between normal and excess of trabeculation in specific cardiomyopathies, despite negative findings in the follow-up of healthy subjects [21].

An additional finding of our study is that T mass and T/C ratio decreased with age, with no correlation with either LV volumes, nor EF. The compact myocardium mass remained stable across age. This might be due to the physiological process of aging. This result was in line with findings from André et al. who also showed a decrease of LV trabeculated mass with age [14]. Dawson et al. suggested a decrease in the T/C thickness ratio with age, using the T/C thickness ratio measured in the end systolic phase with MRI [22], and this trend was confirmed in our study. Lastly, no gender differences have been reported in the literature regarding T/C ratio [7,22], which is in accordance with our results. The T/C ratio has been

shown to be different between ethnic groups and seems to be higher in Chinese and African-American populations [13], therefore our values may be only applicable in Caucasian populations.

The non-compactness of the myocardium has been studied in a large cohort of patients in the MESA study, but was limited to the measurement of the thickness of the compact and trabeculated LV wall [21] or using the global fractal approach [23]. The proposed segmentation tool integrates other crucial functional parameters like EDV and LV wall mass which could help in patients stratification. Indeed, some of these parameters are prone to affect the morphology and amount of LV trabeculations [13,14,20].

Our method has yet to be applied in a larger population, prospectively, using a multicentric design. In our study, only one ethnic group was included.

We have proposed normal values for T, C and T/C mass ratio in a cohort of healthy Caucasian subjects. These normal values of the T/C ratio are 9.1 ± 3.7 % for men and 9.2 ± 5.2 % for women; within each gender, T/C decreases with greater age. While the compact and trabeculated myocardium masses appear to relate to both cardiac function and gender, there was no correlation between these parameters and the T/C ratio.

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Table and figure legends

Table 1. Baseline characteristics of the healthy volunteers (mean±SD & ranges)

Table 2. Left ventricular parameters and masses (mean±SD & 95% CI).

Table 3. Values of T/C ratio for men and women by age groups (mean±SD & 95% CI).

Table 4. Intra-observer & inter-observer variability.

Table 5. Impact of age, gender, ejection fraction and end-diastolic volume on left ventricular masses.

Figure 1. Example of the 16-segments left ventricular segmentation over base (left), median (middle) and apex (right). (a) Epicardial border in blue (manually drawn), endocardial border in red (manually drawn), trabeculae border in green (automatically segmented), papillary muscles in yellow (included in the compact myocardium mass, semi-automatically segmented) and the 16-segments delineations in magenta. (b) To help the operator refine the segmentation of the trabeculae, the original image is displayed with the endocardial and the trabeculae borders (red line). (c) A semiautomatic thresholding tool helps suppress blood (white pixels) and isolate trabeculae (gray pixels). (b) and (c) are zoomed for better visibility.

Figure 2. Influence of age on left ventricular parameters and masses. (a) Distribution of ejection fraction (EF), and (b) end-diastolic volume (EDV) and end-systolic volume (ESV) measurements by age groups. (c) Distribution of left ventricular compact (C) and trabeculated myocardium masses (T), and (d) T/C ratio by age groups. The values are represented as connected means±SD for age groups 20-29, 30-39, 40-49, 50-59 and 60-69 years old. ns, non-significant p value; *, $P=0.0184$; **, $P=0.0003$; ***, $P<0.0001$.

Figure 3. Mean measurement values of the ratio T/C for the 16 LV segments. C, compact myocardium mass ; T, trabeculated myocardium mass.

Conflict of interest:

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

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Statistics and biometry:

One of the authors has significant statistical expertise.

Informed consent:

Written informed consent was obtained from all subjects in this study.

Ethical approval:

Institutional Review Board approval was obtained.

Study subjects or cohorts overlap:

Some study subjects or cohorts have been previously reported in Bricq et al. article (Semiautomatic detection of myocardial contours in order to investigate normal values of the left ventricular trabeculated mass using MRI, JMRI 2015)

Trial registration: clinicaltrials.gov NCT01712581. Registered 17 October 2012.

Table 1. Baseline characteristics of the healthy volunteers (mean±SD & ranges)

	All	Gender groups			Age groups (years)					P-value
		Male	Female	P-value	20-29	30-39	40-49	50-59	60-69	
Height [cm]	170±10[60.9 - 63.9] [149-192]	177±7 [163-192]	163±7 [149-176]	<0.0001*	172±9 [155-187]	170±8 [154-183]	169±12 [150-192]	169±10 [155-189]	169±10 [149-176]	ns [†]
Weight [kg]	70±15[60.9 - 63.9] [45-138]	80±14 [50-138]	61±10 [45-94]	<0.0001*	67±12 [51-110]	69±12 [48-94]	71±16 [47-105]	71±16 [45-103]	74±19 [49-138]	ns [†]
BSA [m ²]	1.80±0.23 [1.40-2.58]	1.96±0.18 [1.57-2.58]	1.65±0.15 [1.40-2.04]	<0.0001*	1.79±0.19 [1.51-2.29]	1.79±0.19 [1.46-2.16]	1.81±0.26 [1.40-2.35]	1.80±0.24 [1.40-2.25]	1.83±0.26 [1.45-2.58]	ns [†]

DCM, dilated cardiomyopathy; BSA, body surface area; SD, standard deviation; *, Mann-Whitney test; †, One-way ANOVA; ns, non-significant P-value.

Table 2. Left ventricular parameters and masses (mean±SD and 95%CI)

	Male	Female	P-value	All
EF (%)	62.4±6.1 [60.9-63.9]	64.9±6.2 [63.4-66.4]	0.0178*	63.6±6.3 [62.6-64.7]
EDV (mL/m ²)	78.8±18.0 [74.5-83.1]	72.8±13.6 [69.6-76.1]	0.0280†	75.8±16.2 [73.1-78.5]
ESV (mL/m ²)	29.8±8.8 [27.7-31.9]	25.9±7.4 [24.1-27.6]	0.0051†	27.8±8.3 [26.4-29.2]
T/BSA (g/m ²)	5.4±2.3 [4.9-6.0]	4.0±2.3 [3.8-4.9]	0.0052†	4.9±2.4 [4.5-5.3]
C/BSA (g/m ²)	60±9.1 [57.8-62.2]	47.7±9.8 [45.4-50.0]	<0.0001*	53.9±11.2 [52.0-55.7]
T/C ratio (%)	9.1±3.7 [8.2-10]	9.2±5.2 [8.0-10.5]	ns*	9.2±4.5 [8.4-9.9]

EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; BSA, body surface area; T, trabeculated myocardium mass; C, compacted myocardium mass; SD, standard deviation; *, Mann-Whitney test; †, t test with Welch's correction; ns, non-significant P-value.

Table 3. Intra-observer & inter-observer variability

Measurement	<i>Intra-observer</i>				<i>Inter-observer</i>			
	Op-1 Segmentation 1 (mean±SD)	Op1- Segmentation 2 (mean±SD)	ICC	Bland-Altman bias* (mean±SD)	Op-1 Segmentation (mean±SD)	Op-2 Segmentation (mean±SD)	ICC	Bland-Altman bias* (mean±SD)
T (g)	6.43±4.28	6.59±4.49	0.99	-0.16±0.39	8.13±4.50	8.77±4.01	0.94	-0.64±1.35
C (g)	82.26±26.02	81.56±25.81	0.98	0.70±2.00	98.06±33.91	101.68±34.00	0.98	-3.61±6.01
T/C ratio (%)	7.65±4.15	7.87±4.32	0.99	-0.21±0.47	7.49±3.23	8.50±2.44	0.80	-0.58±1.81

C, compact myocardium mass; T, trabeculated myocardium mass; *SD*, standard deviation; ICC, intraclass correlation coefficient; *, difference (Op-1 Segmentation 1 – Op-1 Segmentation 2) vs. average

Table 4. Impact of age, gender, ejection fraction and end-diastolic volume on left ventricular masses

Multivariate ANOVA					
	Whole model	Age	Gender	EF	EDV
C	p<0.0001	p=0.67	p<0.0001	p=0.001	p<0.0001
T	p<0.0001	p=0.007	p=0.02	p=0.91	p<0.0001
T/C ratio	p=0.0009	p=0.008	p=0.53	p=0.26	p=0.27

C, compact myocardium mass; T, trabeculated myocardium mass; EF, ejection fraction; EDV, end-diastolic volume.

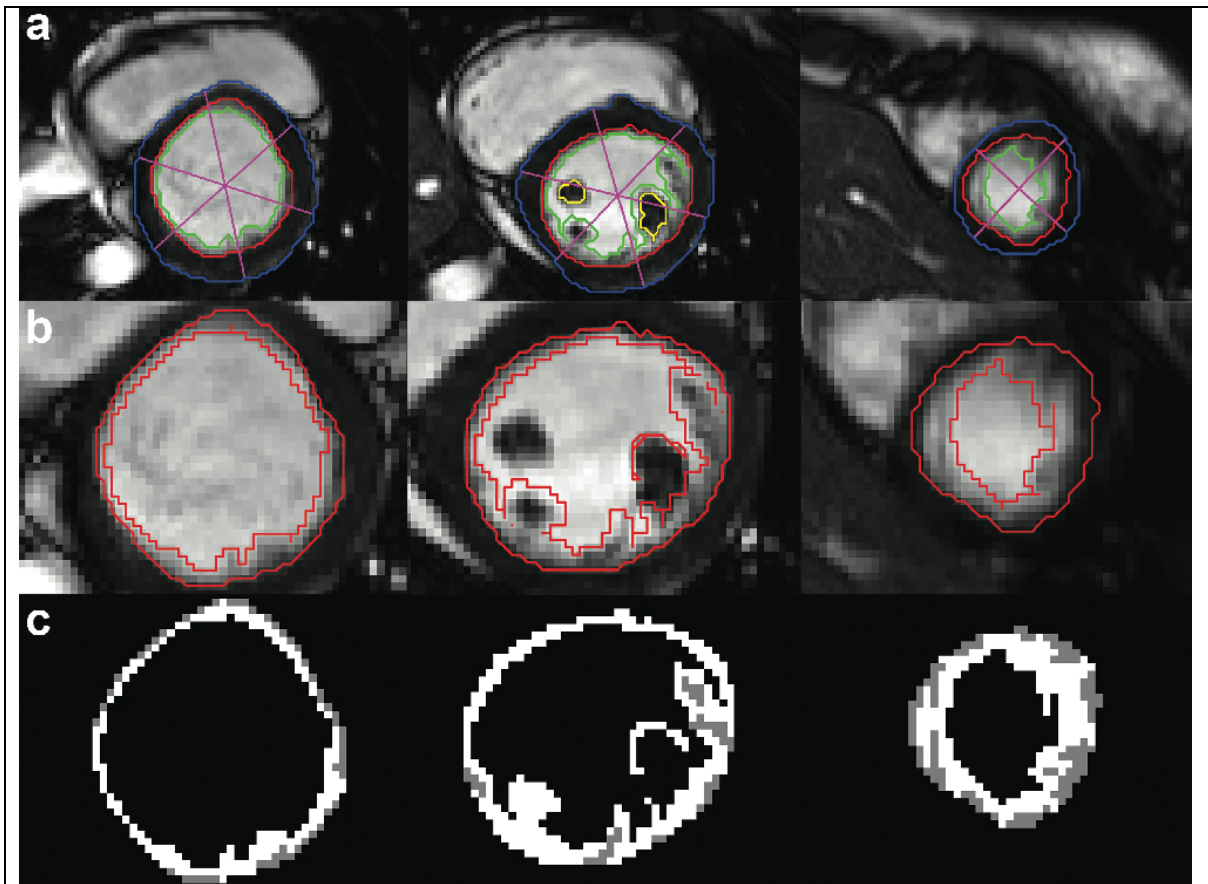


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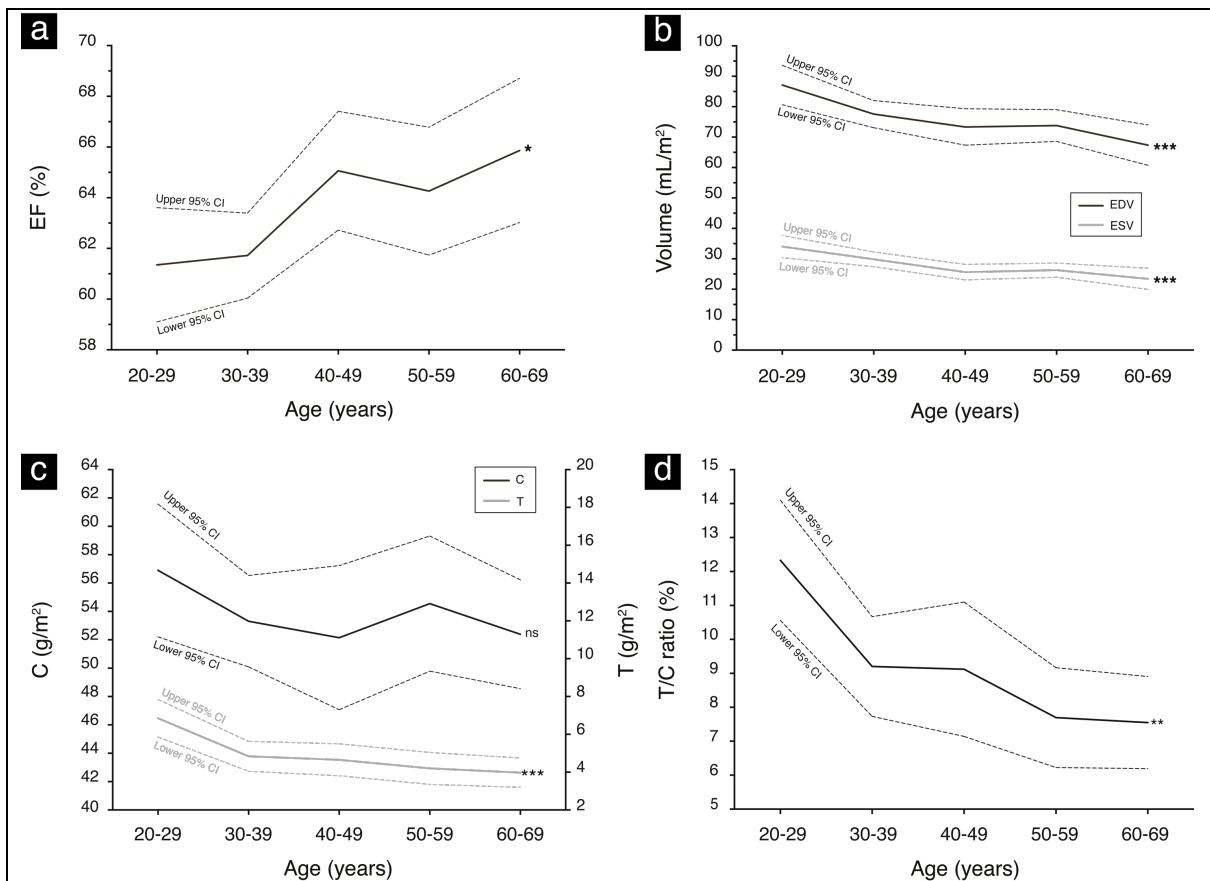


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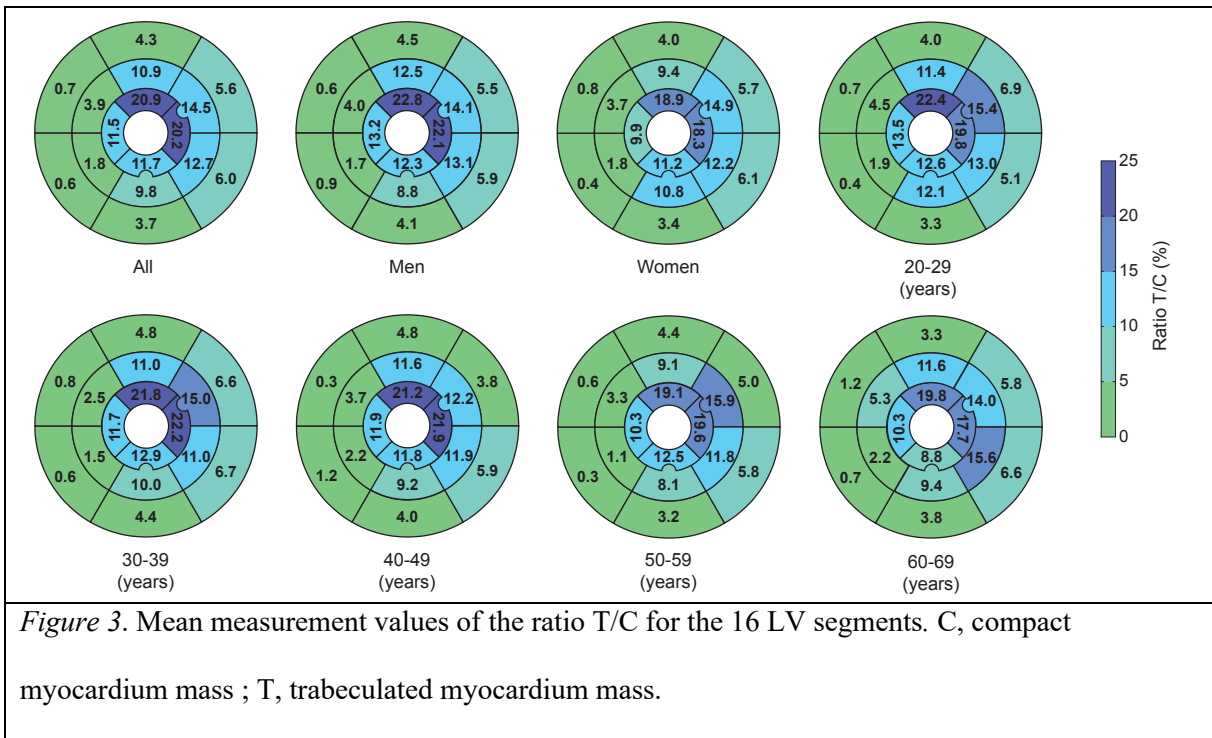


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