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New insights in left ventricular non-compaction cardiomyopathy

DOCTORAL THESIS SUMMARY

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2. **Visoiu IS**, Rimbas RC, Magda LS, Mihaila-Baldea S, Balanescu P, Mihalcea D, Chitroceanu AM, Stefan M, Gheorghiu L, Marinescu AV, Nicula AI, Vinereanu D. Multimodality approach by cardiac magnetic resonance and biological markers in left ventricular non-compaction with heart failure with preserved ejection fraction – revealing the unknown. Eur Heart J - Cardiovasc Imaging 2021; 22: Issue Supplement_1, jeaa356.329. IF 9.130
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1. Bjarke Jensen**, Simona Visoiu**, Roxana Rimbas, Alina Nicula, Dragos Vinereanu. The ventricular trabecular layer operates at a high ejection fraction", *DAP 2023 Annual Meeting* (The Official Meeting of the ESC Working Group on Development, Anatomy and Pathology) Paris, France, 6-8 November 2023

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3. **I.S. Vișoiu**, R.C. Rimbas, L.S. Magda, S. Mihaila-Baldea, D. Mihalcea, A. Chitroceanu, A.I. Nicula, A.V. Marinescu, D. Vinereanu. Left ventricular non-compaction in patients with heart failure with preserved ejection fraction characterized by multimodality imaging. Romanian Journal of Cardiology 2020, Supplement: 9-10

INTRODUCTION

Left ventricular non-compaction was considered initially a primary genetic cardiomyopathy by the American Heart Association in 2006 [1], and later an unclassified cardiomyopathy by the European Society of Cardiology in 2008 [2]. Currently, according to 2023 ESC guidelines, it is no longer considered a distinct cardiomyopathy, but rather just a phenotypic trait [3].

This myocardial phenotype is characterized by prominent trabeculations along the left ventricular (LV) endocardial border, with deep intertrabecular recesses that are part of the ventricular cavity.Thus, the myocardial wall has a bilaminar appearance, with a trabecular layer located subendocardial, and a compact layer located subepicardial [3].

Several terminologies have been used to define this phenotype, from "spongy myocardium" in 1926 to "ventricular noncompaction" today. Morphometric studies in humans show no evidence of a compaction process during gestation, in the sense of coalescence of the trabeculations to form the compact myocardium wall [4]. In the absence of a myocardial compaction process, the terminology of myocardial noncompaction is inappropriate. According to a recent expert panel paper, the terminology that best defines this phenotype is "excessive trabeculation" [5].

Until now, many studies have focused on proposing cut-offs to delineate normal trabeculation from excessive trabeculation of the LV. Multiple diagnostic criteria have been published, with a poor correlation between them [6], with no consensus on which cardiac phase should be used, which cardiac view to choose or what to measure exactly from the layer ratio, the trabeculations number, the trabecular myocardial mass/volume percent, or the complexity of the endocardial border [7].

Despite all these efforts to define excessive trabeculation from a structural point of view, LV trabeculation extent has no prognostic impact [8], making it even more difficult to understand the functional implications of this phenotype. While excessive trabeculation can be found in healthy population cohorts [5], it had also been reported in patients with diverse underlying diseases, from cardiomyopathies and congenital heart diseases to valvular heart diseases, hematological disorders and renal disorders, being associated with an increased risk of heart failure [7].

In this context, this research aims to contribute to the understanding of the functional implications of LV trabeculations.

PERSONAL CONTRIBUTIONS

Characterization of the pathophysiology of left ventricular excessive trabeculation in heart failure with preserved ejection fraction: a multimodal approach (Chapter 6)

6.1 Introduction

The excessive trabeculation phenotype, when present in the LV, has been thought to carry a high risk of heart failure, although it has also been reported in healthy individuals without heart failure [9]. In this context, it is not very clear whether excessive trabeculation is the cause of heart failure or rather its consequence. The pathophysiology of LV excessive trabeculation in heart failure remains elusive and challenging.

We aimed to characterize structural and functional changes in patients with excessive trabeculation of the LV and heart failure, by comparison with patients with heart failure without excessive trabeculation, using biomarkers, echocardiography with speckle tracking analysis and CMR. Since excessive trabeculation is found both in heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), we considered that we could better evaluate the role of trabeculations by analyzing only patients with HFpEF, the etiology of a HFrEF being likely multifactorial.

6.2 Matherial and methods

In this study 21 patients with HFpEF and LV excessive trabeculation were analyzed. HFpEF was defined according to the current guidelines diagnostic criteria [10]. A control group was allocated, which consisted of 21 patients with HFpEF without excessive trabeculation, matched for age and sex. All patients performed speckle-tracking-echocardiography (STE), CMR with T1 mapping, and biomarker assessment for heart failure (NT-proBNP), for myocardial fibrosis (Galectin-3), and for endothelial dysfunction [ADAMTS13, von Willebrand factor (vWf), and their ratio]. By STE, we assessed the longitudinal strain (LS), global, for each LV levels (basal, mid, and apical), and for each LV layer, from epicardium to endocardium. We calculated the base-to-apex gradient, and transmural deformation gradient. By CMR, we assessed native T1 and extracellular volume (ECV), for each LV levels (basal, mid, and apical) and we computed the base-to-apex gradients, as the difference between apical and basal values.

6.3 Results

Patients with excessive trabeculation had higher values for NT-proBNP [237 (156-489) vs. 156 (139-257), *P*=0,04] and Galectin-3 [7.3 (6.0-11.5) vs. 5.6 (4.8-8.3) ng/ml, *P*=0,04], and lower values for ADAMTS13 (767.3±335.5 ng/ml vs. 962.3±253.7 ng/ml, *P*=0.04) and ADAMTS13/vWF ratio [31.3 (14.8-42.3) vs 40.8 (32.0-52.5), *P*=0.03).

The global LS was similar between groups. On the regional level, LS apical was lower in patients with excessive trabeculation (-21.4±4.4% vs. -24.3±3.2%, *P*=0.01), by comparison with the control group (**Figure 6.2., Figure 6.3**), due to significantly lower values of peak LS at the apex, at the apical septal, apical anterior, and apical lateral segments. LS base-to-apex gradient was also lower in patients with excessive trabeculation (3.8±4.7% vs. 6.9±3.4%, *P*=0.02), by comparison with the control group, as was also the LS transmural gradient (3.9±0.8% vs. 4.8±1.0%, *P*=0.006).

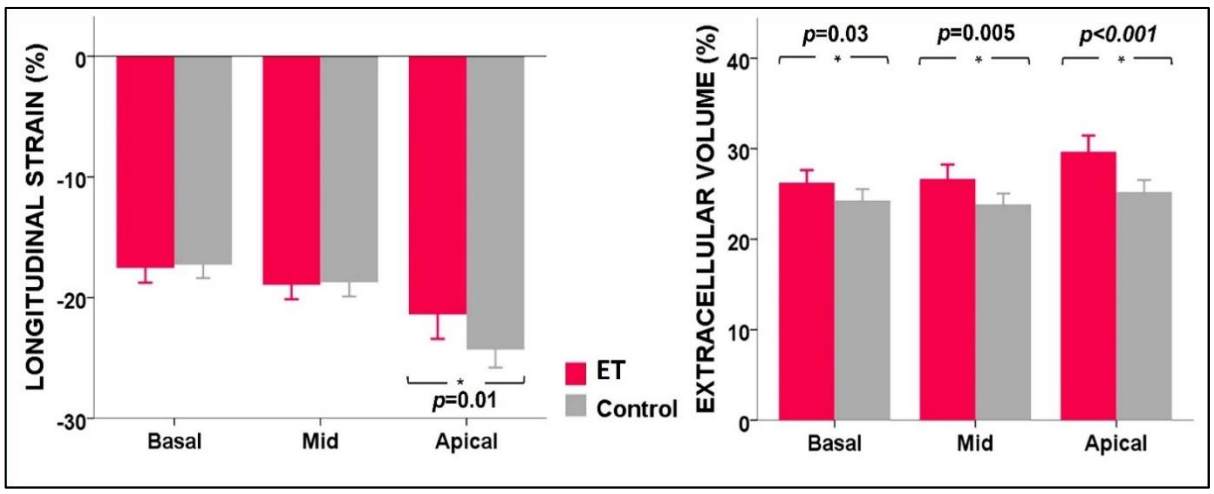

Figure 6.2. Comparison between patients with HFpEF with excessive trabeculation (in pink) and the control group without excessive trabeculation (in grey) by LV levels, using STE and CMR - *adapted from* [11].

In patients with excessive trabeculation, ECV was globally expanded (27.2±2.9% vs. 24.4±2.5%, *P*=0.002), with higher values also at the apical level (29.6±3.8% vs. 25.2±2.8%, *P*<0.001), by comparison with the control group (**Figure 6.2.**, **Figure 6.3.**). ECV base-to-apex gradient was significantly higher in patients with excessive trabeculation [2.8 (1.2-5.6) % vs 0.9 (0.1-2.1) %, *P* = 0,01]. The presence of LGE was not different between the two groups (p=0.63). The percent of trabecular myocardial mass correlated positively with ECV base-to-apex gradient (R=0.555, *P*=0.01), while compact myocardial mass correlated negatively with the ECV base-to-apex gradient (R=-0.639, *P*=0.002). Galectin-3 correlated

positively with native apical T1 time (R=0.490, *P*=0.04) and NT-proBNP (R=0.539, *P*=0.02) in patients with excessive trabeculation. Endothelial dysfunction biomarkers correlated positively with compact myocardial mass (R=0.588, *P*=0.01 for ADAMTS13 and R=0.824, *P*<0.001 for ADAMTS13/vWF ratio).

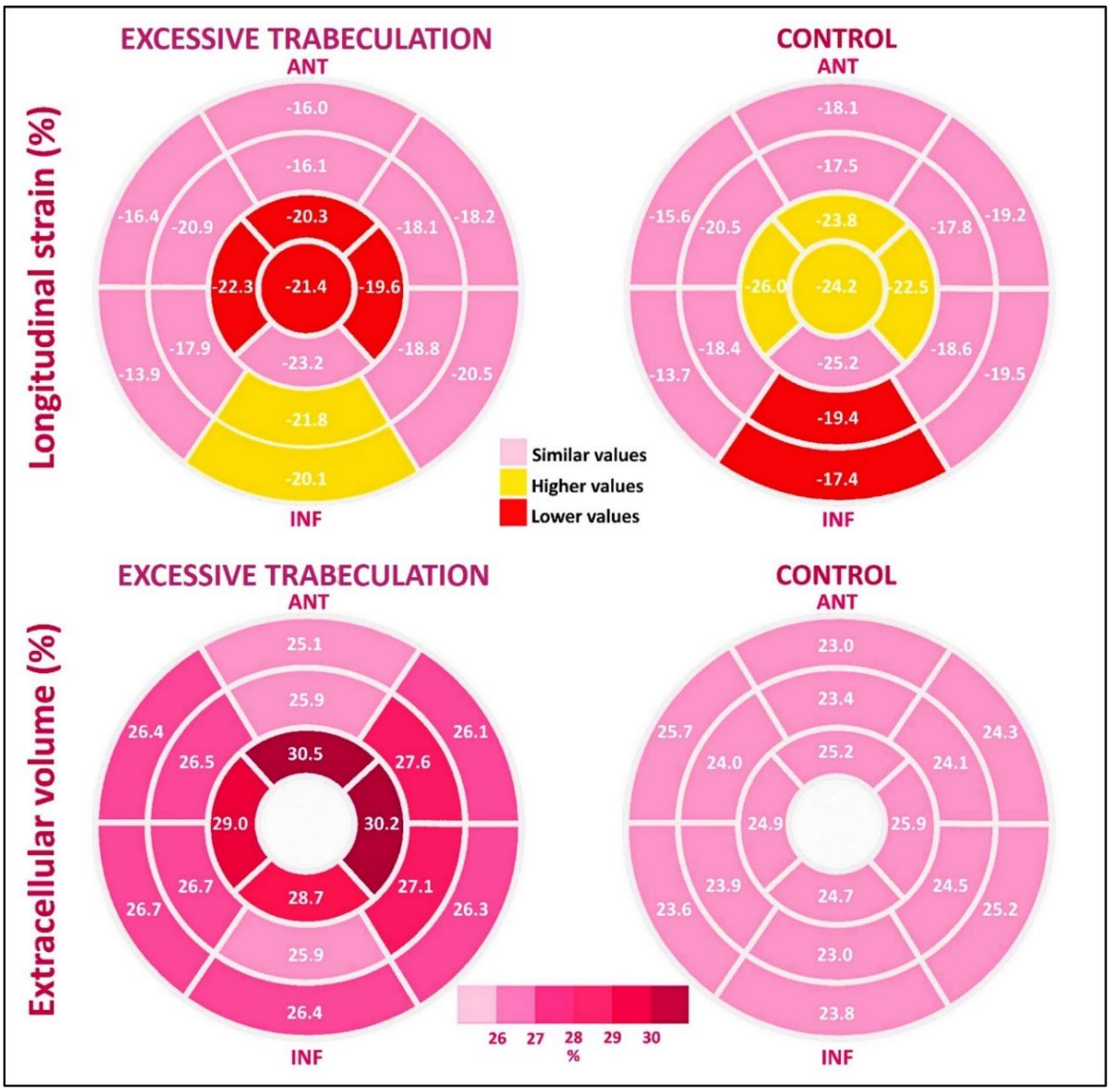

Figure 6.3. Comparison between patients with HFpEF with excessive trabeculation and the control group without excessive trabeculation, by myocardial segments, using STE and CMR - *adapted from* [11].

6.4 Discussions

In this prospective study, by using a multimodality approach, we showed that patients with HFpEF and excessive trabeculation of the LV have higher NT-proBNP values, endothelial dysfunction, higher values of the myocardial fibrosis biomarker, and

significantly decreased longitudinal strain in the apical excessively trabeculated LV segments, associated with increased ECV on CMR.

This is the first study that showed lower levels of ADAMTS13 in patients with excessive trabeculation of the LV. We found positive correlations between ADAMTS13 and compact myocardial mass. Thus, as the compact myocardial mass decreases, ADAMTS13 level decreases, whereas the trabecular myocardial mass increases.

We found higher levels of Galectin-3 in patients with HFpEF and excessive trabeculation. Tissue characterization by T1 mapping showed diffusely expanded ECV, more extensive at the apical level, findings suggestive of myocardial fibrosis. Galectin-3 correlated positively with native apical T1 and NT-proBNP in the setting of excessive trabeculation.

Patients with excessive trabeculation had lower values of LS in the apical segments by comparison with HFpEF controls, with lower values of base-to-apex LS gradient, on the background of apical fibrosis. In accordance with our findings, previous studies reported reduced LS in patients with excessive trabeculation and preserved LVEF, when compared with normal subjects [12,13]. Bellavia et al. [13] also found that LS was more impaired in the apical segments. By assessing the multilayer LS of the compact wall, we found that transmural LS gradient was significantly lower in patients with excessive trabeculation, suggesting a more homogenous contraction in this setting. Similar findings were reported in patients with excessive trabeculation and HFrEF, in a CMR feature tracking study [14].

6.5 Conclusions

Patients with HFpEF and excessive trabeculation of the LV have a worse neurohormonal profile, with higher values of NTproBNP, by comparison with patients without excessive trabeculation. These patients have endothelial dysfunction, expressed by lower ADAMTS13 and ADAMTS13/vWF ratio, and overexpression of Galectin-3, leading to diffuse myocardial fibrosis. The interstitial fibrosis is more advanced at the apical level, explaining the decrease of apical deformation, and thus the lower base-to-apex deformation gradient, with a compensatory increase of the trabecular myocardium. The compact wall has a more homogenous contraction in the presence of trabeculations, with a lower transmural deformation gradient. The findings of this study underpin the idea that excessive trabeculation in HFpEF is an adaptive remodeling phenotype, in the context of a worse neurohormonal profile.

Assessment of left ventricular trabecular layer impact on diastolic function (Chapter 7)

7.1 Introduction

In a normal LV, the trabecular myocardium accounts for about 15% of the total myocardial mass and provide mechanical support during diastolic filling [15]. In the setting of excessive trabeculation, where a significant part of the LV cavity is occupied by trabeculations, the LV compliance may decrease. Some authors reported, in isolated clinical cases, high LV filling pressures in the setting of excessive trabeculation, but on the background of advance heart failure [16]. These authors proposed a partial debridement of the LV trabecular meshwork that may restore both the diastolic and the systolic function [16]. However, in a large cohort of 585 patients, only 64 patients with excessive trabeculation had a diastolic dysfunction grade ≥2 [17]. Moreover, in pregnant women with excessive trabeculation during third trimester, the E/A ratio, the deceleration time of E wave and both the septal and lateral E/e` ratio were not influenced by the extent of trabeculation [18]. The filling pressures, estimated non-invasively by the E/e` ratio were also similar between athletes with and without excessive trabeculation [19].

On this background, it is not very clear what is the impact of trabeculations on LV diastolic function. In this study, we aimed to evaluate the prevalence of diastolic dysfunction and its degree of severity in patients with excessive trabeculation of LV, to further assess the impact of trabeculation extent on the LV diastolic function.

7.2 Matherial and methods

In this prospective study we evaluated 37 patients with excessive trabeculation. NT-proBNP was measured for each patient. All patients performed TTE, STE and CMR. By TTE we measured LV volumes, LV diastolic parameters and left atrium (LA) volumes, based on which we computed the EF of the LA, corresponding to the atrial phasic functions. By STE we measured the LV global longitudinal strain (GLS) and LA phasic functions. We defined diastolic function by two methods:

-method 1: according to the conventional algorithm, based on the 2016 American Society of Echocardiography recommendations [20].

-method 2: using the validated LA reservoir strain categorization of diastolic function [21]: grade 0: LA reservoir strain ≥35%; grade 1: LA reservoir strain ≥24 and <35%; grade 2: LA reservoir strain ≥19 and <24%; grade 3: LA reservoir strain <19%.

Using LA reservoir strain, LAVI max and E/e` we computed LA stiffness index and distensibility index using the available published formulas [22].

By CMR, we assessed LV volumes, LVMI, native T1 time, ECV, and LA volumes. Considering that all patients had a trabecular myocardium/compact myocardium thickness ratio >2.3 in end-diastole in long axis images, to stratify the patients with excessive trabeculation of LV according to trabecular layer extent, we divided the patients in 3 groups (tertiles), based on the trabecular myocardial mass %: Q1<20%, Q2≥20 and <30%, and Q3≥30%.

7.3 Results

All patients had cardiovascular risk factors, hypertension having the highest prevalence (73%), being followed by dyslipidemia (67.6%), obesity (48.6%), diabetes (27%), and smoking (21.6%). Heart failure was present in 83.8% of patients. The most frequent type of heart failure was HFpEF (57%), followed by HFrEF (22%) and HFmEF (5%).

According to the conventional algorithm only 8.1% had a normal diastolic function, 5.4% had an indeterminate diastolic function and 86.5% of patients had diastolic dysfunction. Among the patients with diastolic dysfunction, 53% had grade II diastolic dysfunction, grade I being present in only 16% of cases and grade III in 31% of case.

When patients were stratified in 3 tertiles based on the percentage of trabecular myocardial mass, there was no statistically significant difference between the tertiles regarding LV diastolic function related parameters (**Table 7.1.**). Also, there was no statistically significant difference regarding the distribution of conventional diastolic dysfunction grades between the 3 tertiles (**Table 7.1.**).

Except a significant positive correlation between the trabecular myocardium/compact myocardium ratio and left ventricular end-diastolic volume index (LVEDVI) (R=0.338, *P*=0.041), as a mark of LV compliance, no other correlations were found with diastolic function related parameters. Further, to investigate if LVEDVI was increased solely on the basis of increased intracavitary myocardial mass, we evaluated the impact of trabecular layer extent on stroke volume. There was no difference between the tertiles of trabecular layer extent regarding the stroke volume (**Figure 7.1.**).

Table 7.1. LV diastolic function and other related parameters in the study population, according to tertiles of trabecular layer extent

Variable	Q1	Q2	Q3	*P* value
E (cm/s)	81.7 ± 19.5	79.9 ± 24.9	85.4 ± 26.0	0.850
E/A ratio	1.5 ± 0.9	1.2 ±0.6	1.3 ± 0.5	0.527
e` mean	9.3 ± 2.0	8.9 ± 2.8	8.1 ± 2.8	0.540
E/e' ratio	9.6 ±4.2	9.6 ± 4.1	10.4 ± 3.7	0.875
PASP (mmHg)	35.1 ± 10.6	36.4 ± 10.5	38 ±16.5	0.858
LAVI max (ml/m^2)	49.1 ± 14.6	52.8 ± 28.9	53.2 ± 15.8	0.875
LAVI preA (ml/m^2)	36.9 ± 17.2	37.9 ± 25.1	37.9 ± 13.5	0.992
LAVI min (ml/m^2)	26.9 ± 17.2	26.0 ± 24.2	27.1 ± 13.9	0.988
LA total EF (%)	48.5 ± 15.0	55.4 ± 11.7	51.0 ± 12.1	0.434
LA expansion index (%)	108.8 ± 59.1	137.6 ± 58.8	114.0 ± 44.11	0.397
LA passive EF (%)	26.4 ± 9.2	30.6 ± 7.2	29.6 ±6.6	0.434
LA active EF (%)	31.2 ± 11.6	36.2 ± 12.1	31.1 ± 11.5	0.474
LA reservoir strain (%)	17.8 ± 7.6	24.1 ± 8.1	21.5 ± 7.9	0.157
LA conduit strain (%)	8.1 ± 3.4	11.7 ± 5.0	10.4 ± 5.9	0.258
LA pump strain (%)	10.2 ± 4.5	12.4 ± 4.4	11.8 ± 3.8	0.477
Stiffness Index	0.6 ±0.5	0.6 ± 0.6	0.5 ± 0.3	0.934
Distensibility Index	0.4 ± 0.3	0.6 ± 0.3	0.4 ±0.2	0.288
LVEDVI (ml/m^2)	91.2 ± 37.3	102.2 ± 54.1	107.1 ±41.8	0.693
Native T1 (ms)	1009.6 ± 24.2	1018.1 ± 40.8	1029 ±33.3	0.411
ECV (%)	26.2 ± 2.8	27.1 ± 3.9	28.8 ± 3.1	0.240
Grade I DD (n, %)	4 (12.5)	2 (6.3)	4 (12.5)	0.505
Grade II DD (n, %)	5 (15.6	8 (56.3)	4 (12.5)	0.266
Grade III DD (n, %)	2 (6.3)	1 (3.13)	2 (6.25)	0.757

DD, diastolic dysfunction; ECV, extracellular volume; EF, ejection fraction; LA, left atrium; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; PASP, pulmonary artery systolic pressure; Q, quantile.

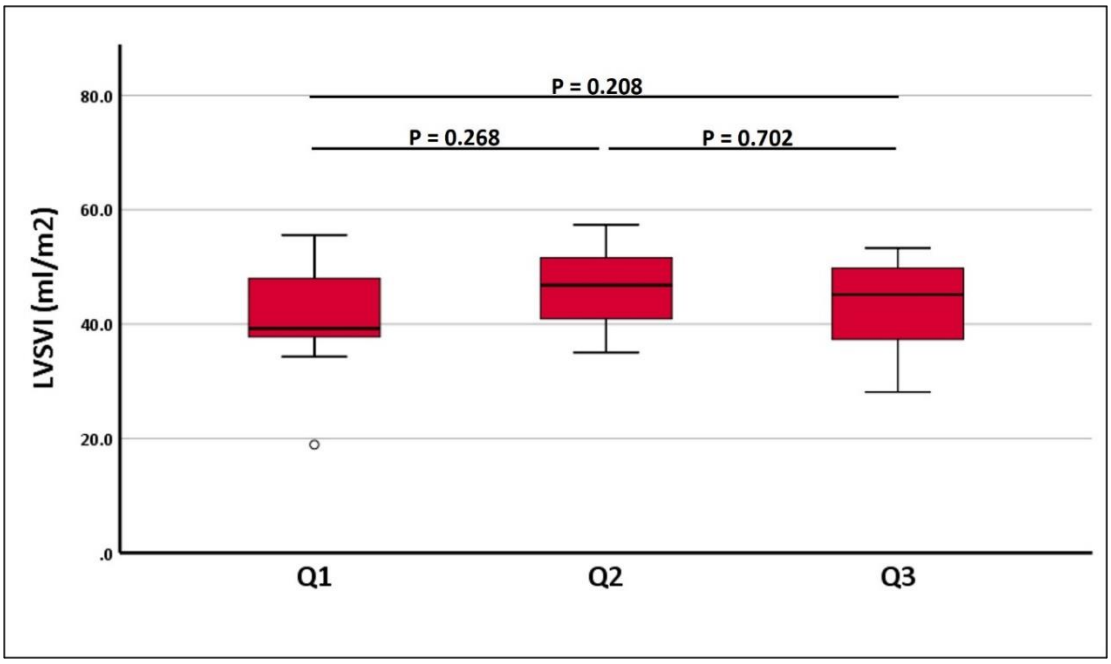

Figure 7.1. Boxplots of LVSVI per tertiles of trabecular layer extent. *LVSVI, left ventricular stroke volume index; Q, quantile.*

According to LA reservoir function classification of diastolic disfunction, 42% of patients fell in grade 1, 22% in grade 2 and 33% in grade 3. Only 3% of patients had a normal diastolic function. There was no difference in trabecular/compact myocardium thickness ratio or trabecular myocardial mass percent across diastolic dysfunction grades (**Table 7.2**).

Table 7.2. Trabecular layer extent across LA reservoir strain DD grades

Variable	Grade 0	Grade 1	Grade 2	Grade 3	*P* value
TM/CM ratio	3.3 ± 0.0	2.9 ± 0.6	3.1 ± 0.7	3.6 ± 1.0	0.124
TMM %	23.4 ± 0.0	25.5 ± 5.5	24.3 ± 12.2	27.4 ± 16.3	0.942

DD, diastolic dysfunction; TM/CM, trabecular myocardium thickness/compact myocardium thickness; TMM%, trabecular myocardial mass % of total LV myocardial mass.

By multiple linear regression analysis, LV filling pressures, assessed non-invasively by E/e` ratio, were best predicted by LA maximal volume (R^2=0.243, *P*=0.012), while LA reservoir strain was best predicted by a model that includes LA pump strain and GLS of the LV (R^2=0.817, *P*<0.001). NTproBNP correlated negatively with both, the LA reservoir strain (R= -0.542, P=0.001) and GLS (R= -0.434, *P*=0.008).

7.4 Discussions

In this study most patients presented diastolic dysfunction, 86.5% using the conventional grading, based on 2016 ASE/EACVI algorithm, or 97% using the LA reservoir strain grading. Using LA reservoir strain diastolic dysfunction grading, the 5% patients with indeterminate function from the conventional algorithm were classified and more than half of patients with grade II diastolic dysfunction have been reclassified.

However, despite the high prevalence of diastolic dysfunction in patients with excessive trabeculation, the LV trabeculation extent, assessed either by trabecular/compact myocardium thickness ratio or trabecular myocardial mass %, remains constant across diastolic dysfunction grades. Also, LV diastolic function parameters remained constant across the tertiles of LV trabecular layer extent.

We found a positive correlation between trabecular myocardium/compact myocardium thickness ratio and LVEDVI, showing an LV adaptation to prevent filling pressure increase. This finding is further supported by the fact that trabecular layer did not impact the filling pressures or the stroke volume. Moreover, LV filling pressures, assessed non-invasively by E/e`, were best predicted by LA maximal volume, whereas LA reservoir strain was best predicted by LA pump strain and GLS of the LV. All patients had cardiovascular risk factors, leading to a high prevalence of HF, of 83.8% in the study population, explaining therefore the presence of diastolic disfunction. Both, the LA reservoir strain and GLS correlated negatively with NTproBNP. All these findings show that LV diastolic disfunction and filling pressures are not related to the extent of trabeculation but to the underlying background.

The results of this study are in agreement with modeling studies results. It was reported that a trabeculated ventricle dilates proportionally with the increase of the trabecular myocardial mass, allowing an adequate stroke volume [23,24]. The presence of trabeculations along the endocardial border increases the intra-ventricular pressure drop, increasing thus the diastolic suction, which should reduce the filling pressure [25].

In a dilated cardiomyopathy study there was no significant statistical difference of E/e` or E/A in patients with or without excessive trabeculation [26].

7.5 Conclusions

The high prevalence of LV diastolic dysfunction in patients with excessive trabeculation is the outcome of the underlying disease, the trabecular layer extent itself not being correlated with LV diastolic dysfunction parameters.

Trabecular layer ejection fraction measurement across the spectrum of LV global systolic function (Chapter 8)

8.1 Introduction

Key prognostic indicators of heart function, such as EDV, SV, LVEF and cardiac output, are currently assessed using TTE or CMR, both in clinical practice and research [27]. Subtle variations in LV structure and function are now being linked to differences in quality of life and incidence of major adverse outcomes, as indicated by the big data analyses [28]. One concern, however, is whether the functional readouts, which are often key prognostic indicators, are measured with the same accuracy across the various ventricular anatomies that the clinician encounters. In echocardiography guidelines and some CMR studies, papillary muscles and trabeculations are deliberately added to the LV blood pool [29,30]. This introduces a bias that affects EF, because the unejectable trabecular tissue is measured as blood. A different bias is introduced when the intertrabecular recesses, which hold LV cavity blood, are added to the myocardial mass [31].

There is then a need to better understand how the trabecular layer contributes to cardiac function. Whether the trabeculations themselves have a poor or good contractility is largely unknown in humans. It is remarkable that some animals with highly trabeculated ventricles and a very thin compact wall can achieve an ejection fraction of 90% [32]. This study aimed to clarify this issue by measuring the ejection fraction (EF) of the trabecular layer.

8.2 Matherial and methods

We assessed 15 patients with excessive trabeculation of LV by CMR. Using a mask/signal threshold to separate cavity from myocardium, the left ventricle was labelled into four regions: compact wall, central cavity, trabeculations, and intertrabecular recesses. For each label we calculated the systolic fractional volume change (SFVC) in short-axis images and systolic fractional area change (SFAC) in 4-chamber images, by dividing end-systolic to end-diastolic values. We measured the EF of the intertrabecular recesses, central cavity, and total cavity. Three different methods to calculate EF of the total cavity were compared: all trabeculations included in cavity (per guidelines), intertrabecular recesses excluded from cavity (Jacquier criterion), all trabeculations are contoured and excluded from cavity (contour-EF).

8.3 Results

The SFVC and SFAC of the compact wall were similar with SFVC and SFAC of trabeculations (both P>0.05). In contrast, the intertrabecular recesses were more diminished in systole by comparison with the central cavity, having lower SFVC (39±17% vs. 56±16%, P<0.001) and SFAC (37±22% vs. 72±12%, P<0.001) (**Figure 8.1.**). EF of the intertrabecular recesses was also greater than EF of the central cavity (61±17% vs. 44±16%, P<0.001) (**Table 8.1.)**. Next, we divided the patient population based on the total cavity EF, as being above or below 50%, and in both of the resultant groups, the EF of the recesses remained significantly greater than that of the central cavity (**Table 8.1.)**.

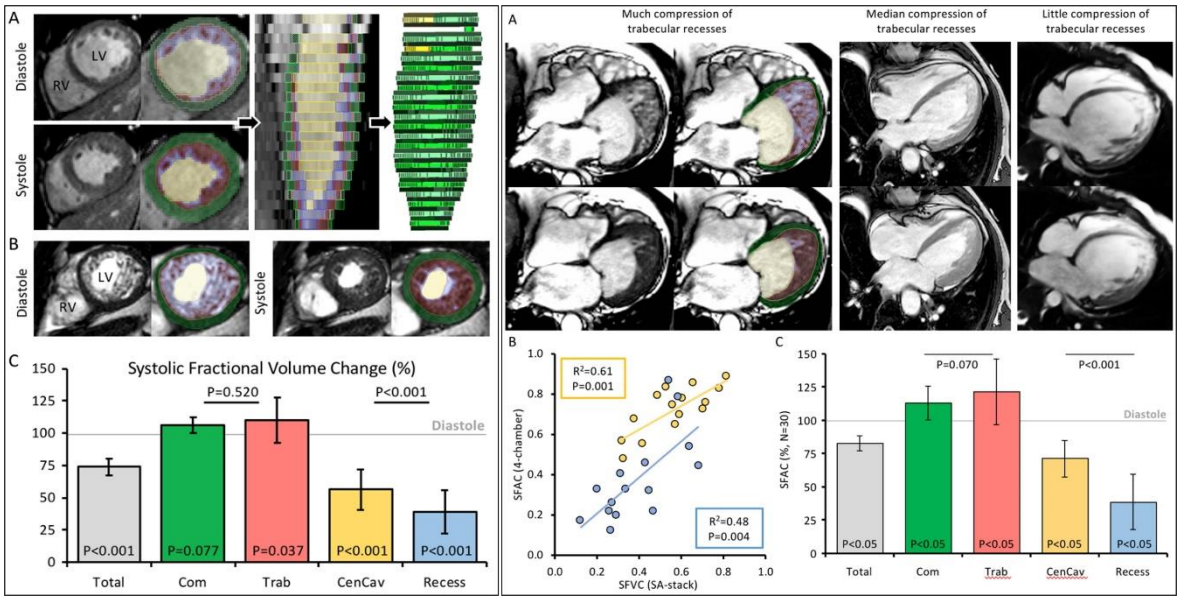

Figure 8.1. Volume (left) and area (right) changes of the four major components of the left ventricle*- adapted from* [33]

Table 8.1. Comparison between the central cavity EF and recesses EF- *adapted from* [33]

Variable	All patients (n=15)	LVEF<50% (n=7)	LVEF>50% (n=8)
Central cavity EF (%)	43.8 ± 15.8	30.6 ± 8.7	55.4 ± 10.2
Recesses EF (%)	61.0 ± 16.7	45.9 ± 9.6	74.3 ± 6.9
P value	<0.001	0.001	0.002

Given the higher EF of the trabecular layer than the central cavity, we next expanded the analysis of our volumetric data to assess the impact of adding the volume of trabeculations to the blood (per guidelines). Compared to the volumes derived from contoured trabeculations, EDV and ESV were increased (**Table 8.2.)**. The SV was not different between the two methods, but given the increased EDV, EF was diminished (40±12% vs. 51±16%, P<0.001) (**Table 8.2.)**. By contouring trabeculations, the number of

patients classified as having severely reduced EF decreases by half (**Figure 8.2.)**. We then assessed the impact of excluding the intertrabecular recesses from the blood pool (per Jacquier criterion) [31]. This was done by subtracting the intertrabecular recesses volume from LV cavity volume, and then we compare these volumes to the volumes derived from contoured trabeculations. All volumes and the EF (44±16% vs. 51±16%, P<0.001) were diminished (**Table 8.2.).**

Table 8.2. Comparison of the three methods of measuring LV volumes and EF

Variable	Trabeculations as blood	Recesses as myocardium	Trabeculations contoured	*P* value[#]	*P* value[##]
EDV (ml)	241.7±93.3	113.3±49.4	193.7±72.4	<0.001	<0.001
ESV (ml)	153.7±81.3	68.8±43.7	102.5±64.8	<0.001	<0.001
SV (ml)	88.3±25.9	44.3±14.5	91.3±24.4	0.293	<0.001
LVEF (%)	39.6±11.8	43.8±15.8	51.3±16.1	<0.001	<0.001

[#]Trabeculations as blood versus trabeculations countered. [##]Recesses as myocardium versus trabeculations contoured

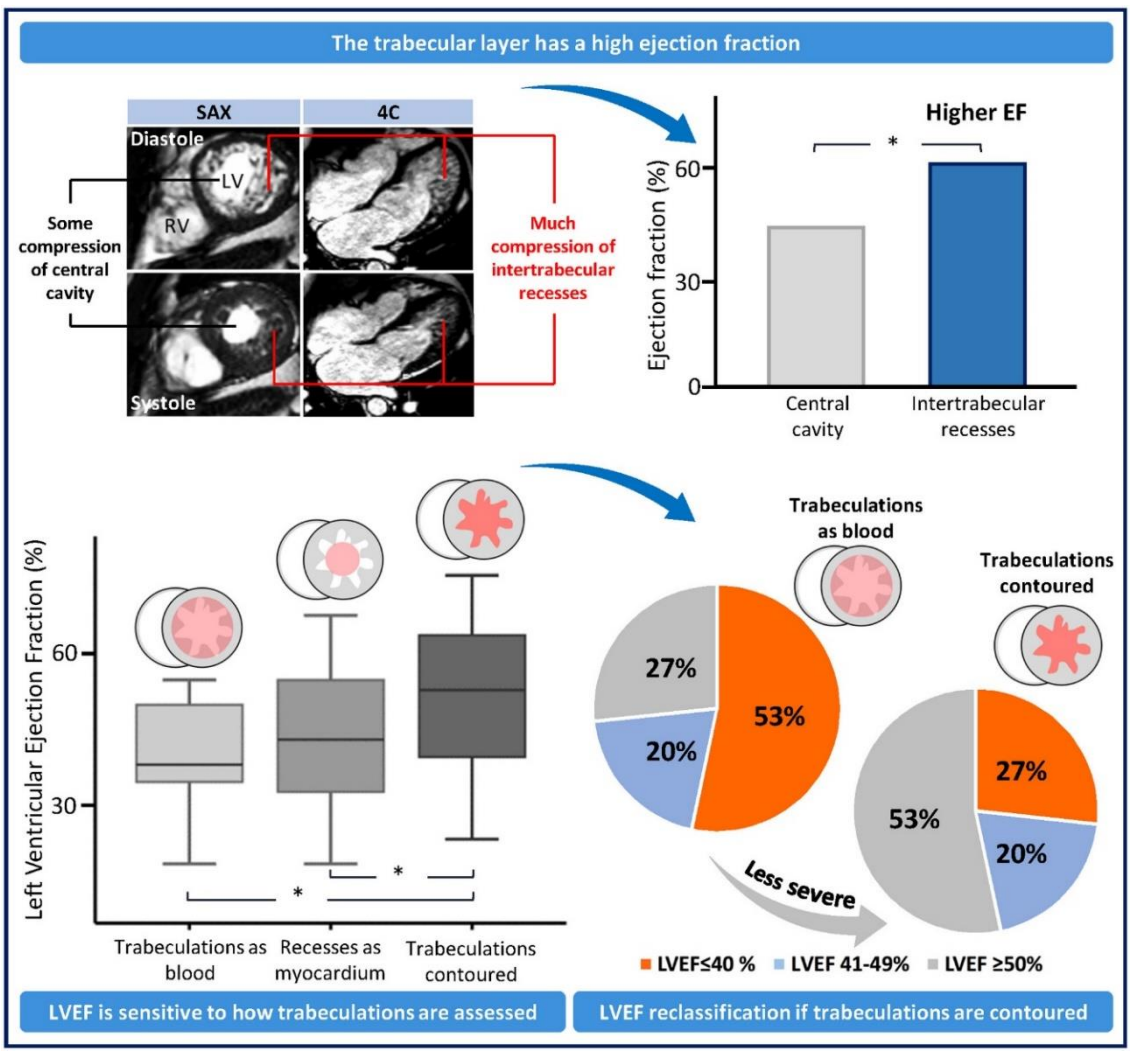

Figure 8.2 Graphical abstract of the study

8.4 Discussions

To the best of our knowledge this is the first study to analyze separately the intertrabecular recesses and the central cavity for the volume changes that occur between diastole and systole. The main finding is that the trabecular layer has a relatively high EF across a broad spectrum of LV function, from severe heart failure to normal pump function. The trabecular layer, however, cannot be analyzed in isolation. We presume that the high EF of the intertrabecular recesses reflects the work done both by the trabecular layer and the compact wall. We show that when ventricular volumes and EF are measured, there is a substantial impact of adding the trabeculations to the LV blood pool, as per guidelines [29], or removing the intertrabecular recesses from the LV cavity, as per a criterion for noncompaction [31]. Only the stroke volume is unaffected, as long as the trabecular mass, that is added to the LV blood pool, is measured to be the same in both end-diastole and end-systole. The method of adding trabeculations to the LV blood pool is ubiquitous in echocardiography where trabeculations cannot yet be reliably contoured. To the extent that important diagnostic choices are made on the basis of EDV, ESV, and EF, the clinician could then consider opting for CMR for higher resolution images and a better assessment.

8.5 Conclusions

The trabecular layer is associated with a high EF. By contouring the trabeculations, LV volumes are more accurately assessed, and implicitly the EF. Stroke volume, in contrast, is not affected as long as the trabecular mass is measured similarly in diastole and systole. The contour-EF, which actually is much higher, could better guide the clinical management in daily practice, avoiding inappropriate diagnosis and treatment.

Conclusions and personal contributions

The presence of trabeculations in the adult human heart still represents a conundrum. Trabeculations are either disregarded when LV functional readouts are measured or overrated when excessive in the LV, being considered a cause of heart failure, ventricular arrhythmias, and systemic thromboembolic events. The purpose of this research was to study the impact of trabeculations on LV function.

In the first study, by comparing patients with heart failure with preserved ejection fraction, with and without excessive trabeculation of the LV, we found that this phenotype represents an adaptive remodeling in the context of a worse neurohormonal profile. Patients with excessive trabeculation had higher NT-proBNP values, endothelial dysfunction expressed by lower ADAMTS13 values, and overexpression of Galectin-3. To the best of our knowledge, this is the first study to show how the interplay between endothelial dysfunction and myocardial fibrosis biomarkers contributes to diffuse myocardial fibrosis, with a greater distribution of increased ECV at the apical level of the LV, in patients with heart failure and excessive trabeculation. The subclinical myocardial fibrosis was the substrate for apical deformation decrease in the compact layer, with a compensatory increase in the trabecular layer extent.

In the second study we evaluated the prevalence of LV diastolic dysfunction in patients with excessive trabeculation of the LV. Despite identifying a high prevalence of diastolic dysfunction, all patients having cardiovascular risk factors, with a high prevalence of heart failure in the study population, the trabecular layer extent itself did not correlate with LV diastolic dysfunction parameters. As the trabecular layer extent increased, LV compliance also increased, having no impact on LV filling pressures or stroke volume.

In the third study we measured for the first time the ejection fraction of the trabecular layer, using a novel CMR method, applying a mask/signal threshold to differentiate myocardium from blood. First, we discovered that trabecular layer operates at a high EF, greater than the central cavity. Second, we found that in the setting of LV excessive trabeculation, there is a bias to a significantly lower LVEF, depending on how the trabecular layer is approached. Since trabeculations cannot be ejected, including trabeculations in the blood volumes, as in current practice, will overestimate the LV volumes, while severely underestimating the LVEF. Stroke volume, in contrast, is not affected as long as the trabecular mass is measured consistently in diastole and systole. When the recesses are added to the trabecular myocardial mass, according to Jacquier criterion, we end up measuring only the central cavity of the LV, underestimating all LV volumes and LVEF. Excluding

trabeculations from the blood volume by contouring the intertrabecular recesses will correct the LV volumes, increasing the LVEF with more than 10%, with a high impact on diagnosis and classification of heart failure.

Taken together, the results of our research show that the trabecular layer does not adversely affect either diastolic or systolic function of the LV. Whether the myocardium is organized in a trabecular or a compact mode, there is no clear evidence to support the inferiority of one to the other. On the contrary, we showed in the third study that trabecular and compact myocardium have a similar area change between diastole and systole, suggesting a similar contractility, explaining thus the high ejection fraction of the trabecular layer, as a collective work of both layers. The equal function of the trabecular and compact myocardium, with a high EF of trabecular layer, irrespective of whether the total LV cavity EF is above or below 50% according to our findings, undermines the notion of a low flow and stasis in the deep intertrabecular recesses, with increased risk of thrombus formation. The high EF of the trabecular layer may also explain the adaptive remodeling phenomenon identified in the first study in patients with HFpEF. Taken together with the higher LV compliance identified in the second study, it may explain the higher stroke volume reported both in modeling and clinical studies in the setting of excessive trabeculation [34].

Also, the findings of a high EF of the trabecular layer, combined with underestimation of LVEF in this setting, may explain the overall good prognosis and the lack of a prognostic significance associated with the extent of trabecular layer itself [34].

LV excessive trabeculation remains a controversial and fascinating subject, with an incompletely elucidated molecular mechanism. We hope that through this research, we have contributed to a better understanding of this phenotype implications in clinical practice.

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