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ORIGINAL PAPER

Left ventricular assessment in patients with systemic light chain amyloidosis: a 3-dimensional speckle tracking transthoracic echocardiographic study

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Abstract

Cardiac involvement in systemic light chain (AL) amyloidosis carries a poor prognosis mainly through involvement of the left ventricular (LV) myocardium. Despite its limitations, two-dimensional transthoracic echocardiography (2D-TTE) remains the main tool used for the assessment of LV systolic function in AL patients. We hypothesize that 3D-TTE coupled with speckle tracking imaging allows earlier detection of LV systolic dysfunction than 2D-TTE in AL amyloidosis. We prospectively studied 71 subjects including 58 patients with confirmed AL amyloidosis (mean age 66 ± 10 years, 60% male) and 21 healthy control (mean age 64 ± 7 years, 48% male) from 2011 to 2014 at the University Hospital of Limoges. The AL patients were divided into three groups according to Mayo Clinic (MC) staging and all subjects underwent 2D-TTE and 3D-TTE at the same setting. Using 2D-TTE, there was no significant difference in LV ejection fraction (EF) between the groups [LVEF = 63 ± 7% (control), 59 ± 6% (MC stage I), 60 ± 8% (MC stage II) and 57 ± 14% (MC stage III) (p = 0.24)]. In contrast, 3D-TTE demonstrated significantly worse LV systolic function in stage II and III patients using 3D-LVEF [MC II and III 45 ± 8% and 39 ± 12% vs. control 53 ± 8% (p < 0.0001)], global longitudinal strain (GLS) [MC II and III − 11 ± 4% and − 8 ± 3% vs. control − 15 ± 3% (p < 0.0001)] and global radial strain (GRS) [MC II and III 14 ± 9% and 10 ± 8% vs. control 25 ± 10% (p < 0.0001)]. Furthermore, MC III patients had significantly worse global circumferential strain and area tracking [− 17 ± 6% and − 25 ± 8% vs. − 24 ± 7% and − 36 ± 7% for control (p < 0.0001)]. Additionally, MC I had significantly better 3D GLS, GRS and global strain (− 15 ± 3%, 25 ± 10% and 28 ± 12%) than MC II (− 11 ± 4%, 14 ± 9% and 16 ± 10%) and MC III patients (− 8 ± 3%, 10 ± 8% and 12 ± 8%), respectively. Despite an apparently preserved LVEF by 2D-TTE, AL patients in MC stage II and III demonstrate evidence of LV systolic dysfunction by 3D imaging using LVEF and strain analysis. Worse LV involvement by AL amyloidosis was associated with more impaired 3D-TTE LV systolic parameters.

Keywords Light chain amyloidosis · 3-Dimensional echocardiography · Left ventricular function

Introduction

Systemic light chain (AL) amyloidosis is a rare but serious disease associated with a poor prognosis that is primarily related to the degree of cardiac involvement [1]. The diagnosis of AL amyloidosis is often delayed since symptoms such as asthenia, dyspnea and lower limb edema are not disease-specific. Consequently, a research effort was done to identify cardiac markers of AL amyloidosis in order to improve risk stratification of patients. In this regard, the Mayo Clinic (MC) staging, based on the N-terminal pro-brain natriuretic peptide (NT-pro BNP) and troponin levels, allows for the accurate classification of patients according to three stages of severity [2]. Nevertheless, this classification

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remains subject to drawbacks, such as in patients with renal failure, since these two biological markers are elevated in this condition. This fact underlies the need for more specific cardiac marker(s) in order to better assess cardiac involvement in AL amyloidosis patients.

In patients with suspected cardiac AL amyloidosis, transthoracic echocardiography (TTE) remains the first line of cardiac imaging. Global and homogeneous increase in left ventricular (LV) wall thickness associated with early diastolic abnormalities and preserved ejection fraction (LVEF) are frequently observed in AL amyloidosis patients. An expert consensus proposed that the diagnosis of cardiac AL amyloidosis can be based on the concomitant finding of an elevated NT-pro BNP (> 312 ng/l) in the absence of renal failure and a mean LV wall thickness ≥ 12 mm [3]. However, the above parameters are not specific for this disease and such an increase in wall thickness already represents a significant degree of LV involvement with the disease process. Furthermore, early stages of cardiac involvement in AL amyloidosis are associated with preserved LVEF.

The development of 2-dimensional speckle tracking imaging (2D-STI) led to the finding that cardiac AL amyloidosis is associated with a reduced LV global longitudinal strain (GLS). Furthermore, this parameter is a predictor of mortality in this patient population [4]. However, the clinical use of 2D-STI is limited by the requirement for 2-, 3- and 4-chamber view sequential acquisition that can be time consuming [5, 6]. The recent development of 3D-STI allows for simultaneous and comprehensive assessment of LV systolic functional parameters with consideration of 3D cardiac motion, which remains limited with 2D-STI.

The objective of the present study is to assess LV systolic function using 3D wall motion tracking imaging derived from TTE in patients with AL amyloidosis.

We hypothesize that 3D-TTE coupled with STI allows for earlier detection of LV systolic dysfunction than 2D-TTE in patients with AL amyloidosis.

Methods

Using the database of the French National Centre for AL amyloidosis, we prospectively identified 71 consecutive patients with confirmed systemic AL amyloidosis who were diagnosed between March 2011 and January 2014 (Fig. 1). Thirteen patients were excluded from the analysis including those with non-AL amyloidosis (four patients with TTR amyloidosis), localised amyloidosis (five patients), suboptimal acoustic windows (three patients) and missing clinical data (one patient). Patients with significant left-sided valvular heart disease (as assessed using the most current recommendations) were not included [7], Consequently, the final study population included 58 AL patients. All patients provided consent to be included in the study. The study was performed in compliance with the Helsinki Declaration.

The diagnosis of amyloid deposition was histologically proven by organ biopsy (minor salivary glands, gingiva, rectum, skin or subcutaneous adipose tissue from the abdominal wall) that demonstrated typical apple-green birefringence when stained with Congo red and viewed under polarizing microscopy. The type of amyloidosis was established by the presence of a monoclonal population of plasma cells in the bone marrow and the identification of monoclonal light chains in the serum and/or urine by immune-fixation electrophoresis [1, 8].

Cardiac involvement was defined according to the standard criteria of the 10th International Symposium on Amyloid and Amyloidosis in 2005 and updated in 2012 [9]. Organ involvement was determined according to established criteria [10]. All patients underwent a complete clinical assessment and physical examination. Clinical data (New York Heart Association [NYHA] functional class and number and type of organ involvement by amyloidosis) and comorbidities (history of hypertension,

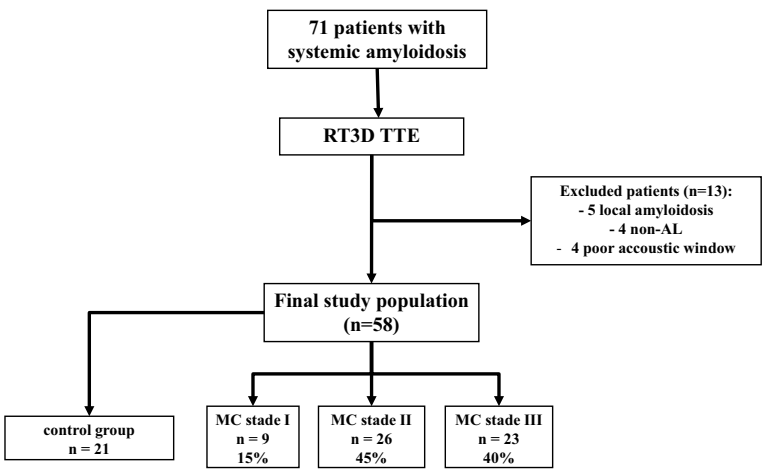

Fig. 1 Study flow chart

diabetes mellitus, dyslipidemia, smoking, coronary artery disease, stroke or chronic renal failure) were prospectively entered in a database. Hypertension was defined as systolic and diastolic blood pressure > 140 mmHg or > 90 mmHg, respectively [11], or as the use of anti-hypertensive therapy. Chronic renal failure was defined as a plasma creatinine level > 170 µmol/l or creatinine clearance < 50 ml/m^2 (Fig. 2).

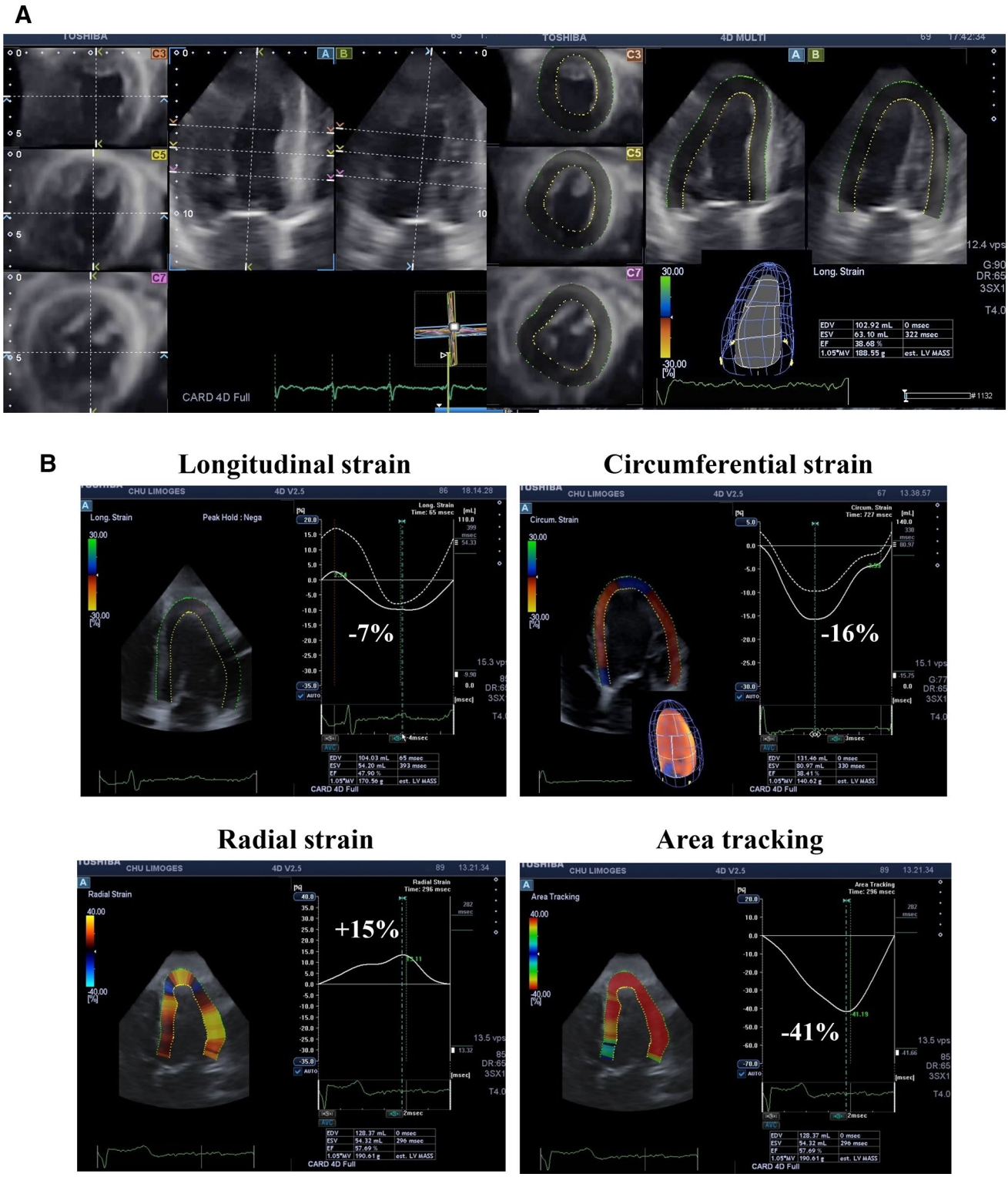

Fig. 2 3-Dimensional speckle tracking analysis in representative patients with cardiac amyloidosis

Biological data (creatinine, delta free light chain, cTnT or cTnI or high sensitivity troponin [hsTn], NT-proBNP or BNP levels) were also performed. An electrocardiogram (ECG) was obtained at the same day as the transthoracic echocardiogram (TTE) and biological data.

A comprehensive evaluation for the type of cardiac amyloidosis was also performed including bone marrow biopsy, serum and urine electrophoresis and immune-fixation, and measurement of serum free light-chain immunoglobulins (Freelite, Binding site).

Mayo Clinic staging

Patients were classified according to the Mayo Clinic prognostic staging as recommended using the three following stages: stage I = normal levels of both biomarkers (NT-pro BNP < 332 ng/l and troponin T < 0.035 µg/l); stage II = only one of the two biomarkers abnormally elevated; and stage III = both biomarkers abnormally elevated.

Control group

A control group with 21 subjects was recruited from our echocardiographic laboratory during the same period as the AL group. These subjects had a normal TTE and were free from cardiac disease.

Echocardiography

All patients underwent a comprehensive TTE including conventional M-mode, Doppler and 2D assessment. In addition, 3D TTE, including 3D-STI analysis, was performed in order to assess LV geometry and function. All echocardiographic studies were performed using the Artida, Toshiba Medical Systems, Tustin, CA, 2011 and the 2D probe (2D PST-30BT) and the 3D probe (PST-25 SX, 2.5 MHz) respectively. Doppler and 2D echocardiographic data were collected following the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommendations [12]. These included: (1) LV end-diastolic and end-systolic diameters in the parasternal long axis view; (2) LV end-diastolic thickness of the interventricular septum and posterior wall; (3) LV ejection fraction using the modified Simpson's biplane method; (4) diastolic LV function assessment using the transmitral E/A ratio and E/E′ ratio obtained at the lateral mitral annulus; (5) Tissue Doppler S-wave velocity at the lateral mitral annulus; (6) left atrial (LA) size using the end-systolic volume in the 4- and 2-chamber views; (7) tricuspid annular plane systolic excursion (TAPSE); (8) S-wave velocity at the lateral tricuspid annulus; (9) systolic pulmonary arterial pressure (sPAP) derived from the tricuspid regurgitation velocity added to the estimated right atrial pressure.

In order to acquire 3D LV parameters, we used the 3D wall motion tracking software. This recent echocardiographic method associates 3D volume acquisition with time-curve derived 3D deformation analysis, thus allowing the automatic tracking of the whole volume of a given cardiac cavity over time and the generation of a time-volume curve along with phasic deformation data. 3D LV volumes are obtained by RT3D from the apical 4-chamber view using the 3D matrix-array transducer (PST-25 SX, 2.5 MHz). As recommended, four cardiac cycles with a 5-s breath hold were required for the acquisition that is triggered by the electrocardiographic R-wave [5]. Four smaller real-time volumes, acquired from alternate cardiac cycles, were combined to provide a larger pyramidal volume. To optimize the frame rate of acquisition between 20 and 30 Hz, depth was minimized to include only the LV. The 3D images of the LV wall were automatically divided into 16 segments. The software automatically tracked the contour on the subsequent frames in three different vectors simultaneously to calculate each strain data. The strain data were obtained by calculating the mean value in each segment. From 3D data set, LV end-systolic and end-diastolic volumes, LV mass and LV ejection fraction were derived. In addition, LV global longitudinal, circumferential and radial strain (GLS, GCS and GRS, respectively) and LV area tracking were automatically calculated with no additional acquisition. The LV global 3D-STI is available on the Artida machine and is provided by the manufacturer. This new strain parameter records the deformation of the myocardial fibers beyond the radial plane. It allows measuring the additional speckle displacement of the radial fibers in the perpendicular planes, thus taking into account fiber shortening beyond the transverse myocardial deformation.

Statistical analysis

Patients were divided into three groups according to the MC stage. Continuous data were expressed as mean ± SD and were compared using 1-way Anova. A Tuckey post-hoc test was used to identify differences between groups. Categorical data were provided as numbers and percentages and were compared using the Chi-2 test or Fisher exact test. Forty-four patients were randomly selected and 3D parameters were measured by two blinded observers (DM and SP) and inter-observer variability was tested. The Bland–Altman analysis was performed to visually estimate the inter-observer variability and mean absolute and relative difference (± SD) were reported. The coefficients of correlation between the two observers were also reported as well as interclass correlation coefficient (ICC).

Statistical analyses were performed using JMP software version 10.0.0, 2012 (SAS Institute Inc., Cary, NC, USA).

Results

Among the 58 patients included in the final analysis of this study (mean age 66 ± 10 years, 60% of males), 9 (15%), 26 (45%) and 23 (40%) were in MC stage I, II, and III, respectively. The control group subjects (n = 21) were free of comorbidities and risk factors for coronary artery disease and were comparable with the AL amyloidosis patients in terms of age, gender and body mass index.

Patients in MC stage III had a higher incidence of hypertension, NYHA functional class III–IV, history of atrial fibrillation and low QRS voltage on the ECG as compared to MC stage I as well as a higher rate of diabetes as compared to MC stage II (Table 1). A trend for a gradual decrease in creatinine clearance was noted with advancing MC stages (p = 0.08). No other significant differences were observed between the three groups regarding demographic data, comorbid conditions, ECG and biological data (Table 1).

Two-dimensional and Doppler echocardiography

There was no significant difference between the control group and MC stage I group regarding LV dimensions, LV function, LA size, right ventricular (RV) size and function or sPAP. In contrast, and as compared to the control group, patients in MC stages II or III had significantly thicker interventricular septum and posterior wall, larger LA diameter and volume, higher LV mass, and worse diastolic parameters with higher E/A and E/E′ ratio. They also had significantly lower TAPSE, higher sPAP and higher incidence of pericardial effusion.

Patients in MC stage I had significantly lower interventricular septal thickness, lower E/E′ ratio, smaller LA volume, lower TAPSE and lower sPAP as compared to patients in MC stages II or III. Only patients in MC stage III showed significantly lower tricuspid annular S-wave velocity and higher rate of pericardial effusion than the control and MC stage I groups. Furthermore, patients in MC stage III showed significantly thicker interventricular septum and posterior wall, higher LV mass and higher rate of pericardial effusion

Table 1 Demographic, clinical, ECG and biologic data

Variables	Whole cohort (n = 58)	MC stage I (n = 9, 15%)	MC stage II (n = 26, 45%)	MC stage III (n = 23, 40%)	p-value
Demographic data					
Age, years	66 ± 10	61 ± 5	67 ± 11	66 ± 11	0.24
Male gender, %	60	67	50	70	0.34
BMI, kg/m²	24 ± 4	25 ± 4	23 ± 3	24 ± 4	0.43
Comorbidities					
Hypertension, %	24	0	23†	35†	0.04
Diabetes, %	7	0	0	17‡	0.02
Smoking, %	16	11	15	17	0.90
Dyslipidemia, %	25	22	27	26	0.96
Stroke, %	3	0	4	4	0.70
NYHA class ≥ III, %	22	0	15	39†	0.01
Renal failure, %	41	22	35	57	0.13
Previous treatment, %	62	56	65	61	0.86
Interval diagnostic/TTE, months	23 ± 29	17 ± 23	30 ± 34	17 ± 26	0.28
ECG data					
Low voltage, %	48	11	58	52†	0.03
Heart rate, bpm	81 ± 15	78 ± 12	80 ± 12	83 ± 19	0.63
Atrial fibrillation, %	14	0	8	26†	0.05
Biological data					
Creatinine, µmol/l	175 ± 202	176 ± 269	156 ± 207	199 ± 165	0.77
Creatinine clearance, ml/min/1.73m²	57 ± 32	71 ± 35	62 ± 33	45 ± 29	0.08
Δ Free light chain, mg/l	186 ± 286	197 ± 213	112 ± 150	268 ± 408	0.18
Δ Light chain, %	71	44	73	79	0.42

AL amyloidosis, *MC* Mayo Clinic stages, *BMI* body mass index, *NYHA* New York Heart Association, *TTE* transthoracic echocardiography

†Significant difference (p < 0.05) with MC stage I

‡Significant difference (p < 0.05) with MC stage II

than patients in MC stages II (Table 2). Interestingly, there was no significant difference between the control group and various MC stages groups in regard to LV diameters and 2D LV volumes, ejection fraction and cardiac output. Only MC stage II and III demonstrated significantly reduced mitral annular S-wave velocity than control healthy subjects (Table 2).

Three-dimensional wall motion tracking echocardiography

There was no significant difference between the control group and MC stage I group in regard to 3D LV dimensions and function (Table 3). However, MC stage II and III patients showed significantly more compromised 3D-LV ejection fraction, GLS, GRS and 3D-global LV strain than the control group. Additionally, MC stage III patients had significantly higher 3D LV end-systolic volume, GCS and area tracking than control.

Patients in MC stage I group had significantly better 3D LV GLS, GRS and 3D-global LV strain than MC stage II and III group and better 3D LV ejection fraction, GLS, GCS, area tracking, and GRS than MC stage III group (Table 3). As compared to MC stages III, patients in MC stages II demonstrated significantly better 3D LV ejection fraction, GLS, GCS and area tracking.

Since atrial fibrillation leads to irregularity in cycle length, we have conducted an additional analysis that included only AL patients in sinus rhythm. The results did not alter our findings and continued to demonstrate a strong relationship between 3D-strain, NYHA functional class and MC staging (NYHA class III and IV vs. I and II: 6.9 ± 3% vs. 12 ± 4%, $p < 0.0001$; MC Stage 1 vs. 2 vs. 3: 15 ± 3%, 11 ± 4%, 8.3 ± 4%, $p < 0.0001$).

Reproducibility

Analysis of the Bland–Altman plots revealed excellent reproducibility for 3D LV strain parameters (Fig. 3). Table 4 demonstrates the average difference of the measurements performed by the two observers. The best ICC was found

Table 2 Two-dimensional and Doppler echocardiographic data

Variables	Controls (n = 21)	MC stage I (n = 9, 15%)	MC stage II (n = 26, 45%)	MC stage III (n = 23, 40%)	p
LV dimensions					
LVED diameter, mm	46 ± 6	46 ± 4	45 ± 7	44 ± 7	0.72
LVES diameter, mm	29 ± 5	29 ± 3	29 ± 5	30 ± 6	0.88
LVED volume, ml	81 ± 27	70 ± 14	77 ± 26	85 ± 22	0.47
LVES volume, ml	33 ± 16	29 ± 8	32 ± 12	36 ± 17	0.58
IV septum, mm	10 ± 1	11 ± 2	13 ± 3*†	16 ± 3*†‡	< 0.0001
Posterior wall, mm	10 ± 2	10 ± 2	12 ± 2*	15 ± 3*†‡	< 0.0001
LV mass, m²	89 ± 25	107 ± 37	127 ± 38*	166 ± 43*†‡	< 0.0001
LV function					
LV ejection fraction, %	63 ± 7	59 ± 6	60 ± 8	57 ± 14	0.24
Cardiac output, l/min	5.6 ± 0.9	6.6 ± 3.2	5.7 ± 2.1	5.2 ± 2.3	0.41
E/A ratio	0.94 ± 0.3	1.04 ± 0.4	1.74 ± 1.4*	1.9 ± 1.2*	0.01
Lateral E/E′ ratio	6.7 ± 2	7.3 ± 2.9	13.8 ± 6.7*†	16.7 ± 9.6*†	< 0.0001
Lateral mitral S-wave, cm/s	9.4 ± 2	8.7 ± 2	7.1 ± 2.5*	6.4 ± 3.4*	0.003
LA size					
LA diameter, mm	33 ± 6	39 ± 5	41 ± 9*	43 ± 6*	0.0001
LA volume, ml/m²	22 ± 7	22 ± 8	35 ± 11*†	39 ± 12*†	< 0.0001
RV function					
TAPSE, mm	22 ± 4	23 ± 5	19 ± 4*†	17 ± 5*†	0.0008
Lateral tricuspid S-wave, cm/s	12.8 ± 1.6	14.1 ± 1.5	12 ± 3.1	10.7 ± 3.2*†	0.01
Systolic PAP, mmHg	26 ± 3	26 ± 8	35 ± 11*†	35 ± 12*†	0.001
Pericardial effusion, %	0	11	36*	71*†‡	< 0.0001

LVED left ventricular end-diastolic, *LVES* left ventricular end-systolic, *IV* interventricular, *LA* left atrium, *TAPSE* tricuspid annular plane systolic excursion, *PAP* pulmonary arterial pressure

*Significant difference ($p < 0.05$) with control group

†Significant difference ($p < 0.05$) with MC stage I

‡Significant difference ($p < 0.05$) with MC stage II

Table 3 Three-dimensional echocardiographic data

Variables	Control (n = 21)	MC stage I (n = 9, 15%)	MC stage II (n = 26, 45%)	MC stage III (n = 23, 40%)	p-value
LV dimensions (ml)					
LVED volume	79 ± 21	88 ± 16	87 ± 26	92 ± 24	0.29
LVES volume	38 ± 14	44 ± 14	47 ± 17	57 ± 21*	0.0004
LV function (%)					
LV ejection fraction	53 ± 8	51 ± 10	45 ± 8*	39 ± 12*†‡	< 0.0001
LV GL strain	− 15 ± 3	− 15 ± 3	− 11 ± 4*†	− 8 ± 3*†‡	< 0.0001
LV GC strain	− 24 ± 7	− 22 ± 7	− 21 ± 5	− 17 ± 6*†‡	0.003
LV area tracking	− 36 ± 7	− 35 ± 7	− 30 ± 7	− 25 ± 8*†‡	< 0.0001
LV GR strain	+ 26 ± 10	+ 25 ± 10	+ 14 ± 9*†	+ 10 ± 8*†	< 0.0001
LV global strain	+ 28 ± 9	+ 28 ± 12	+ 16 ± 10*†	+ 12 ± 8*†	< 0.0001

LVED left ventricular end-diastolic, *LVES* left ventricular end systolic, *GL* global longitudinal, *GC* global circumferential, *GR* global radial

*Significant difference ($p < 0.05$) with control group

†Significant difference ($p < 0.05$) with MC stage I

‡Significant difference ($p < 0.05$) with MC stage II

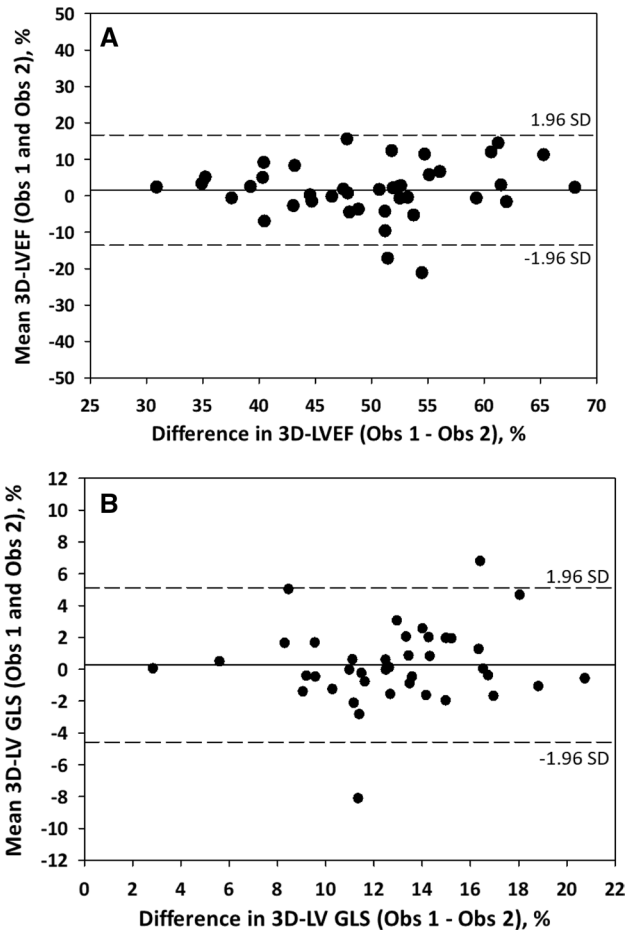

Fig. 3 Bland Altman graphs showing inter-observers reproducibility for 3-dimensional left ventricular ejection fraction (LVEF, **a**) and left ventricular global longitudinal strain (LV GLS, **b**)

Table 4 Interobserver variability for 3D echocardiographic data

Variables	Average of differences	Relative average of difference (%)	r	ICC
LV ejection fraction, %	0.9 ± 0.8	2 ± 15	0.84	0.83
LV GL strain, %	0.36 ± 0.3	0.2 ± 23	0.87	0.89
LV GC strain, %	0.07 ± 0.6	1.6 ± 27	0.71	0.67
LV GR strain, %	1.5 ± 0.9	4.4 ± 50	0.73	0.70
LV Area tracking, %	1.6 ± 0.8	4.5 ± 24	0.73	0.67
LV global strain, %	2.5 ± 0.9	5.1 ± 39	0.71	0.69

ICC interclass correlation coefficient, *LVED* left ventricular end-diastolic, *LVES* left ventricular end systolic, *GL* global longitudinal, *GC* global circumferential, *GR* global radial

with 3D LV GLS. All others 3D parameters showed good reproducibility with high ICC (all > 0.67).

Discussion

To our knowledge, our study is the first report of systemic AL amyloidosis to analyze all LV deformation parameters using RT3D wall motion tracking according to the Mayo Clinic prognostic staging. We demonstrate that patients with systemic cardiac AL amyloidosis have significantly impaired LV systolic function as assessed by 3D TTE whereas conventional 2D TTE fails to demonstrate any evidence of LV systolic dysfunction. Patients with the worst cardiac involvement in AL amyloidosis (i.e., those in MV stage II and III) demonstrated marked reduction in 3D LV ejection fraction, GLS, GCS, GRS and area tracking. In addition, reproducibility analysis revealed good inter-observer variability.

LV systolic function in patients with AL amyloidosis

The conventional LV ejection fraction derived from modified Simpson's biplane method using 2D echocardiography does not allow the differentiation of patients according to MC staging. Accordingly, LV ejection fraction was not significantly worse in patients with AL amyloidosis as compared to the control group. However, the mitral annular S-wave velocity, a marker of LV longitudinal function, was gradually impaired in higher MC stage. Similar data was reported by Koyama et al. in 97 patients with AL amyloidosis [13]. In their study, LV longitudinal function was altered in patients with heart failure despite a preserved LV ejection fraction. Indeed, in AL amyloidosis patients, LV ejection fraction remains reasonably preserved despite biological evidence of increased LV wall stress and myocardial injury.

Recent advances in deformation imaging using strain derived from 2D speckle tracking analysis demonstrated the ability to recognize the presence of subclinical LV systolic dysfunction via the identification of impairment in longitudinal function. Furthermore, speckle tracking appears to be more accurate in the identification of subclinical LV dysfunction than tissue Doppler imaging [14]. After adjustment for clinical, biological and echocardiographic predictors of survival, a GLS worse than − 12% carries a significant negative impact on survival, thus emphasizing the importance of integrating GLS measurement in clinical practice [4].

In patients with AL amyloidosis, our data confirm the association of, not only the GLS with the MC prognostic staging, but also of other LV deformation parameters. However, the association of all 3D strain parameters with mortality in AL amyloidosis needs further and larger outcome studies.

Additionally, our data confirm previous findings and demonstrate that 3D echocardiographic parameters are more accurate than 2D parameters in the assessment of the cardiac consequences of AL amyloidosis. Patients in MC stage II, an intermediate stage of cardiac involvement, demonstrated significantly lower 3D LV ejection fraction and longitudinal and radial strain, findings that were not evident on 2D TTE, thus emphasizing the usefulness of these 3D-derived parameters.

Another finding in our study is the high reproducibility of measuring 3D LV parameters in our patient population and recent literature is consistent with this finding. Despite a learning curve for new imaging modalities, the measurement of LV function by 3D TTE appears to be easy, rapid and accurate, which may suggest that this modality is ready for clinical practice.

Clinical implications

Given that 3D LV function assessment allows for the identification of early and subclinical LV dysfunction, we recommend its use in clinical practice for the management of patients with AL amyloidosis. Despite a preserved 2D LV ejection fraction, the subtle myocardial consequences of AL amyloidosis appear to be unmasked by assessment of 3D echocardiographic parameters, particularly using strain imaging, even in patients in the MC stage II. These patients exhibit a significantly lower 3D longitudinal and radial strain than control subjects or MC stage I patients. Consequently, an earlier imaging diagnosis of LV dysfunction may allow for earlier treatment in this patient population. While any resulting impact on outcome requires further studies, it is possible that an earlier treatment of patients with AL amyloidosis depicting a reduced LV longitudinal or radial function could be of benefit.

In a similar manner, the adverse impact of the disease on LV myocardial function as assessed using 3D TTE may promote a more aggressive therapeutic strategy in patients in group MC stage III. In fact, some patients in this group have a significant poor LV longitudinal (i.e., worse than 5%) or radial (i.e., < 10%) strain, likely indicating a more advanced stage of the disease and worse degree of myocardial damage. An appropriately aggressive therapeutic approach in these patients might be of value.

Following the introduction of therapy, a regular clinical and echocardiographic follow-up of AL amyloidosis patients is crucial. Evaluation of LV systolic parameters using 3D TTE and speckle tracking-derived parameters can be useful to assess more accurately the changes in myocardial function following treatment.

We believe that the use of 3D TTE as a tool for the therapeutic management of AL amyloidosis patients, in addition to MC staging, is appealing. However this hypothesis will need to be validated in a large randomized clinical trial. Meanwhile, it is reasonable to use 3D TTE for the assessment of LV function in order to unmask early and subtle LV damage.

Limitations

Our results were obtained in a relatively small sample size, particularly for patients in the MC stage I group (n = 9). Additionally, our institution is a tertiary referral center, thus bias is expected with significantly sicker patients being referred. This may lead to erroneous conclusions related to type II error and limited statistical power. Nevertheless, this limitation is not likely to impact the main findings of our study that focuses on the relationship between the degree of

cardiac involvement in AL amyloidosis and worsening 3D LV functional parameters.

It is important to realize that 3D TTE has several limitations. First, it does not allow for optimal image acquisition in patients with poor acoustic windows. Furthermore, its low frame rate may lead to inaccurate sampling in patients with rapid heart rate and/or irregular rhythm such as sinus tachycardia or atrial fibrillation. Patients' cooperation is required for a breath hold that spans 4 cardiac cycles. Finally, it is time consuming and requires more technical expertise than 2D-TTE.

Another limitation of our study relates to the definition of systemic hypertension. Our patients were recruited between 2011 and 2014, prior to the publication of the current hypertension guidelines in 2017. Therefore we have followed the recommendations of the published guidelines during that period for the definition of hypertension [11].

Another limitation involves the MC staging of patients that is based on the NT-pro BNP and troponin levels. These biomarkers are known to increase in the setting of advanced renal failure, and the latter may influence the classification of patients according to the stage. However, there was no significant difference between the three MC stages and the frequency of renal failure in our patient population. Furthermore, the fact that 3D echocardiography demonstrated a progressive impairment in LV myocardial function with higher MC stage suggests that this classification is not significantly impacted by renal failure in our patient cohort.

Conclusion

In patients with AL amyloidosis and preserved LV systolic function as assessed by conventional 2D echocardiography, 3D TTE may unmask global, longitudinal, circumferential and radial LV myocardial abnormalities. A graded relationship was identified between increased AL amyloidosis-related cardiac impairment severity, as clinically assessed using MC staging, and worsening of 3D LV function parameters. With its high rate of reproducibility, 3D TTE appears to provide additional information than 2D TTE for the assessment of AL amyloidosis patients. Nonetheless, larger studies are required to determine the prognostic value of 3D-STI-derived parameters in this patient population.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All ethical standards were respected during this work.

Research involving human and animal rights No animals were involved in our study.

Informed consent Informed consent was obtained from all individual participants included in the study.

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