IJC Heart & Vasculature 40 (2022) 101026

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

The tricuspid annulus in amyloidosis with cardiac involvement: Detailed analysis from the three-dimensional speckle tracking echocardiographic MAGYAR-Path Study

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ARTICLE INFO

Keywords:
Cardiac amyloidosis
Tricuspid annulus
Three-dimensional
Echocardiography

ABSTRACT

Introduction: Amyloidosis is a rare condition due to extracellular deposition of excessive amount of protein in parenchymal tissues including the heart. The present study aimed to test whether cardiac amyloidosis (CA) is associated with morphological and functional abnormalities of the tricuspid annulus (TA). For this aim, the results of patients having CA were compared to age- and gender-matched healthy controls by three-dimensional speckle-tracking echocardiography (3DSTE). Moreover, differences in TA parameters between light-chain CA (AL-CA) and transthyretin CA (TTR-CA) were studies as well.

Materials and Methods: The study comprised 27 CA patients (mean age: 62.7 ± 9.1 years, 21 males), their results were compared to those of 20 age- and gender-matched healthy volunteers (59.3 ± 3.8 years, 13 males). Complete two-dimensional Doppler echocardiography and 3DSTE were performed in all CA patients and controls.

Results: Dilated end-diastolic and end-systolic TA diameter, area and perimeter could be detected in all CA patients and in the AL-CA and TTR-CA subgroups, as well. Although only a few TTR-CA patients were involved, morphologic TA parameters proved to be tendentiously higher as compared to those of AL-CA patients. Functional parameters of TA were found to be reduced in CA patients, which were more deteriorated in AL-CA patients.

Conclusions: Dilated TA is associated with its functional deterioration in CA.

1. Introduction

Amyloidosis is a rare condition due to extracellular deposition of an abnormal protein produced in excessive amount in parenchymal tissues including the heart [1–4]. Cardiac amyloidosis (CA) is known to be associated with reduced systolic and diastolic left ventricular (LV) function and increased interventricular septum thickness. However, increased right heart dimensions and wall thickness and reduced right heart function could also be detected in CA patients using routine echocardiographic methods [1]. The tricuspid valve is positioned between the right atrium (RA) and ventricle (RV) and has a significant role in flow management between these chambers. The tricuspid valve is a complex structure incorporating the annulus (TA), three leaflets and the subvalvular apparatus (chordae tendinae, papillary muscles). The TA is an asymmetric, saddle-shaped fibrous ring having a dynamic motion throughout the cardiac cycle [5]. Recent non-invasive imaging techniques including three-dimensional speckle-tracking echocardiography (3DSTE) allow detailed spatial assessment of TA respecting the cardiac cycle [6,7]. The present study aimed to test whether CA is associated with morphological and functional abnormalities of TA. For this aim, their results were compared to age- and gender-matched healthy controls by 3DSTE. Moreover, differences in TA parameters between light-chain CA (AL-CA) and transthyretin CA (TTR-CA) were studies as well.

2. Materials and methods

2.1. Patient population

The study comprised 27 CA patients (mean age: 62.7 ± 9.1 years, 21 males), their results were compared to those of 20 age- and gender-matched healthy volunteers (59.3 ± 3.8 years, 13 males). CA was

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https://doi.org/10.1016/j.ijcha.2022.101026
Received 24 January 2022; Received in revised form 25 March 2022; Accepted 1 April 2022

defined in accordance with the current consensus criteria and practices [8,9]. In the CA group, 16 patients had hypertension, 9 patients had hypercholesterolaemia and 2 patients had diabetes mellitus. Biopsy was carried out in all patients to confirm the diagnosis of CA. The first positive biopsy site was the myocardium in 7 cases, bone marrow in 6 cases, duodenum and rectum in 5 cases, salivary gland in 1 case, skin and subcutaneous tissue in 2 cases and kidney in 10 cases in the CA patients. In 5 CA patients, biopsy samples were collected from more than one organ. CA proved to be light-chain amyloidosis (AL-CA) in 21 subjects and transthyretin amyloidosis (TTR-CA) in 6 patients. Diagnosis of multiple myeloma was confirmed in 16 out of 21 AL-CA patients. If extracardiac biopsy was found to be positive for amyloid, the following echocardiographic criteria were used (unexplained LV wall thickness ≥ 12 mm + 1 or 2) [9]:

Characteristic echocardiography findings ($\geq$2 of a, b and c have to be present):

a. Grade 2 or worse diastolic dysfunction.

b. Reduced tissue Doppler s′, e′, and a′ wave velocities (<5 cm/s).

c. Decreased LV global longitudinal strain (absolute value $< -15\%$).

Multiparametric echocardiographic score ≥ 8 points:

a. Relative LV wall thickness (interventricular septum + LV posterior wall)/LV end-diastolic diameter > 0.6 (3 points)

b. Doppler E wave/e′ wave velocities > 11 (1 point).

c. Tricuspid annular plane systolic excursion ≤ 19 mm (2 points).

d. LV global longitudinal strain (absolute value) $\leq -13\%$ (1 point).

e. Systolic longitudinal strain apex to base ratio > 2.9 (3 points).

The present study is a part of the **M**otion **A**nalysis of the heart and **G**reat vessels b**Y** three-dimension**A**l speckle-t**R**acking echocardiography in **Path**ological cases **(MAGYAR-Path) Study**, in which valvular annular parameters were assessed among others in different disorders by 3DSTE. Informed consent was given by all patients and controls, the study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institution's human research committee.

2.2. Two-dimensional Doppler echocardiography

Routine two-dimensional echocardiographic examinations were performed with a Toshiba Artida™ system (Toshiba Medical Systems, Tokyo, Japan) using a 1–5 MHz PST-30SBP phased-array transducer according to the available guidelines including chamber quantifications and Doppler measurements [10]. Significant valvular regurgitations and stenoses were excluded by the aid of Doppler together with assessment of mitral inflow E/A. Degree of valvular regurgitations were assessed according to the international standards [11].

2.3. 3DSTE-derived data acquisitions

The same Toshiba Artida™ echocardiographic tool (Toshiba Medical Systems, Tokyo, Japan) using PST-25SX matrix-array transducer (Toshiba Medical Systems, Tokyo, Japan) was used. During data acquisitions, 6 wedge-shaped subvolumes were collected from an apical window during a single breath-hold. All subjects were in sinus rhythm. To obtain the best spatial resolution for endocardial border, delineation sector width was chosen to be as narrow as possible [6,7]. 3D echocardiographic datasets were acquired and analysed by experienced observers (ÁK, GR).

2.4. 3DSTE-derived TA assessments

TA measurements were performed by 3D Wall Motion Tracking software version 2.7 (Toshiba Medical Systems, Tokyo, Japan). Using acquired 3D echocardiographic dataset, the software automatically selected apical two- (AP2CH) and four-chamber (AP4CH) views and 3 short-axis views at different LV levels at end diastole. AP2CH and AP4CH views were used to help to find the optimal endpoints (edges) of the MA on C7 short-axis view. End-diastolic (just before mitral valve closure) and end-systolic (just before mitral valve opening) measurements were performed to calculate the following morphological and functional TA parameters (Fig. 1) [12–14]:

Morphological parameters.

-TA diameter (TAD), measured by drawing a perpendicular line from the peak of TA curvature to the middle of the straight TA border,

-TA area (TAA), measured by planimetry,

-TA perimeter (TAP), measured by planimetry,

Functional parameters.

-TA fractional shortening (TAFS), defined as ([end-diastolic TAD - end-systolic TAD]/end-diastolic TAD) × 100,

-TA fractional area change (TAFAC), defined as ([end-diastolic TAA - end-systolic TAA]/end-diastolic TAA) × 100.

2.5. Statistical analysis

Continuous variables were reported as mean ± standard deviation and tested for normality. Student's *t*-test was used for datasets following normal distribution and Mann-Whitney-Wilcoxon test was used for datasets that were not normally distributed. Categorical variables were expressed as counts and percentages and Fisher's exact test was used to compare them. A value of $p < 0.05$ was considered to be statistically significant. For statistical analysis, MedCalc software (MedCalc, Mariakerke, Belgium) was used.

3. Results

3.1. Demographic and two-dimensional echocardiographic data

CA patients had significantly higher LA diameter, smaller LV end-diastolic diameter, thicker interventricular septum and LV posterior wall and increased E/A ratio compared to the results of healthy controls (Table 1). None of the 27 CA patients and their matched controls had atrial fibrillation in their medical history. In the CA group, 10 patients had no mitral regurgitation (MR), 10 patients had mild MR and 7 patients had moderate MR. Tricuspid regurgitation (TR) was detected in 15 patients, 7 patients had mild TR, 4 patients had moderate TR, 4 patients had severe TR. In the control group, 19 patients had no MR, 1 patient had mild MR. TR was present in 1 patient, its severity was mild. None of the CA patients and controls showed significant valvular stenosis.

3.2. 3DSTE-derived TA parameters

Dilated end-diastolic and end-systolic TA diameter, area and perimeter could be detected in all CA patients and in the AL-CA and TTR-CA subgroups, as well. Although only a few TTR-CA patients were involved, morphologic TA parameters proved to be tendentiously higher as compared to those of AL-CA patients. Functional parameters of TA were found to be reduced in CA patients, which were more deteriorated in AL-CA patients (Table 2).

4. Discussion

3DSTE is capable not only for volumetric and functional assessment of ventricles and atria [6,7], but for non-invasive evaluation of annular dimensions of atrio-ventricular valves as well [14,15]. Although mitral and tricuspid valves have a special 3D shape, 3DSTE-derived measurements allow only their 2D-projected 'en-face' assessment in one plane. This type of evaluation is relatively simple, only planes could be optimized on valvular edges as demonstrated above. Due to the limited nature of 2D echocardiography in assessing the tricuspid valve and its annulus, 3D echocardiography offers new insight into the valvular dynamics during the cardiac cycle via a simple non-invasive way [5,12–14]. Moreover, disease-specific alterations could be theorized due to specific volumetric and functional properties of certain disorders.

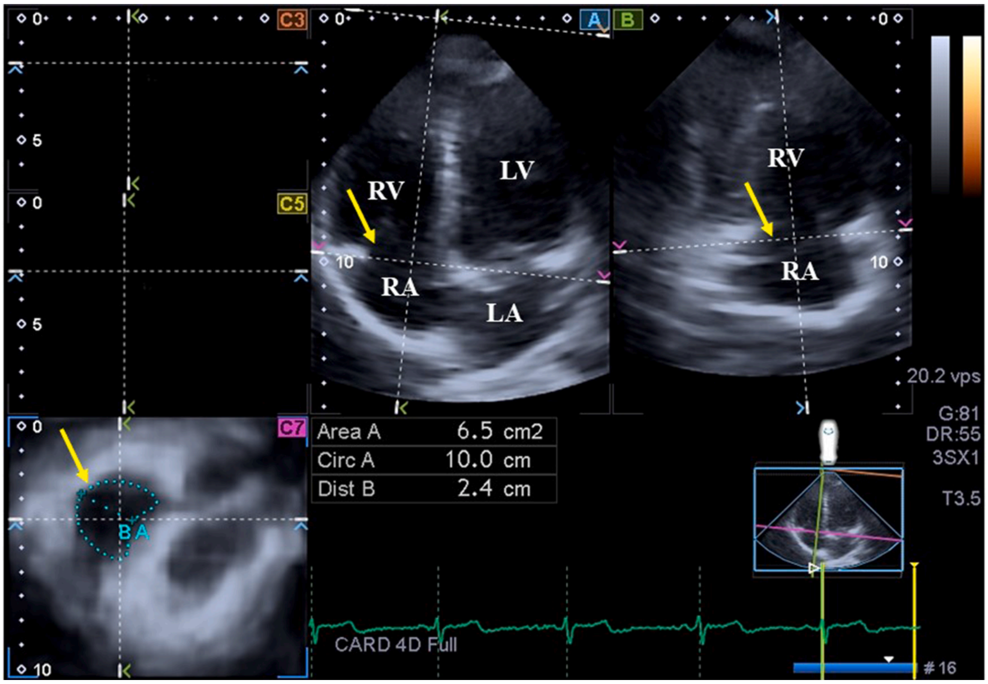

Fig. 1. Extract from a three-dimensional full-volume dataset demonstrating the tricuspid annulus (TA) in a patient with cardiac amyloidosis: apical four-chamber view (A); apical two-chamber view (B); and a cross-sectional view at the level of the tricuspid annulus optimized in apical four- and two-chamber views (C7). The yellow arrow represents the tricuspid annular plane. **Abbreviations:** LA, left atrium; LV, left ventricle; TA, tricuspid annulus; RA, right atrium; RV, right ventricle; Area, TA area; Circ, TA perimeter; Dist, TA diameter. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Two-dimensional echocardiographic data in patients with cardiac amyloidosis and controls.

	Controls (n = 20)	CA patients (n = 27)
LA diameter (mm)	40.2 ± 3.6	46.1 ± 8.5*
LV end-diastolic diameter (mm)	48.7 ± 3.4	46.0 ± 4.7*
LV end-diastolic volume (ml)	111.5 ± 16.8	104.1 ± 27.2
LV end-systolic diameter (mm)	31.5 ± 3.9	30.0 ± 5.2
LV end-systolic volume (ml)	37.0 ± 8.6	40.0 ± 17.0
Interventricular septum (mm)	9.3 ± 1.1	15.2 ± 3.7*
LV posterior wall (mm)	9.3 ± 1.0	14.0 ± 2.7*
LV ejection fraction (%)	66.9 ± 4.8	60.8 ± 13.1
E (cm/s)	74.9 ± 16.2	82.9 ± 22.3
A (cm/s)	72.7 ± 17.0	58.4 ± 29.1
E/A	0.98 ± 0.4	1.92 ± 1.3*

*$p < 0.05$ vs. Controls **Abbreviations:** CA = cardiac amyloidosis, E and A = early and late diastolic transmitral flow velocities, LA = left atrial, LV = left ventricular.

Congestive heart failure, atrial and ventricular arrhythmias, conduction abnormalities, orthostatic hypotensive episodes, and autonomic dysfunction are common cardiac complications in CA [16]. Increased interventricular septum thickness, decreased LV-EF and Doppler velocity E/e' ratio suggesting abnormal systolic and diastolic LV function could be seen in CA [1]. In recent 3DSTE studies, detailed analysis confirmed significant abnormalities in LV rotational mechanics with 60% ratio of near absence of LV twist (LV 'rigid body rotation') [17] with reduced LV strains [18] and enlarged LA volumes and functional deteriorations [19]. Associated with these alterations, MA proved to be dilated and functionally impaired [20].

In the right heart, RA enlargement and increased RV wall thickness were found with increased inferior vena cava diameter. Tricuspid annular plane systolic excursion (TAPSE), as a functional feature of RV systole, was very poor in CA [1,9,16]. Detailed 3DSTE-derived RA analysis confirmed increased RA volumes respecting the cardiac cycle and abnormalities in RA emptying fractions and strains characterizing systolic reservoir and late-diastolic active booster pump RA functions [21]. Moreover, RV dysfunction was found to be associated with more severe LV involvement in AL amyloidosis with higher plasma levels of

Table 2
Comparison of three-dimensional speckle-tracking echocardiography-derived tricuspid annular morphological and functional parameters between patients with cardiac amyloidosis and controls.

	Controls (n = 20)	all CA patients (n = 27)	AL-CA patients (n = 21)	TTR-CA patients (n = 6)
Morphological parameters:				
TAD-D (cm)	2.1 ± 0.2	3.0 ± 0.6*	2.9 ± 0.5*	3.3 ± 0.7*
TAA-D (cm^2)	6.1 ± 1.1	10.7 ± 3.5*	10.1 ± 3.3*	12.8 ± 3.5*
TAP-D (cm)	9.8 ± 1.0	12.5 ± 2.0*	12.2 ± 2.0*	13.6 ± 1.9*
TAD-S (cm)	1.6 ± 0.2	2.6 ± 0.6*	2.6 ± 0.6*	2.9 ± 0.8*
TAA-S (cm^2)	4.1 ± 1.0	8.0 ± 3.2*	7.5 ± 2.9*	9.5 ± 3.7*
TAP-S (cm)	8.0 ± 1.0	10.6 ± 2.1*	10.3 ± 1.9*	11.8 ± 2.4*
Functional parameters:				
TAFAC (%)	32.0 ± 11.1	26.1 ± 11.2†	25.7 ± 10.5†	27.1 ± 14.3
TAFS (%)	21.6 ± 7.4	12.8 ± 10.3*	11.9 ± 10.4*	16.0 ± 9.8

Abbreviations: D = end-diastolic, S = end-systolic, CA = cardiac amyloidosis, AL-CA = light-chain cardiac amyloidosis, TTR-CA = transthyretin cardiac amyloidosis, TAD = tricuspid annular diameter, TAA = tricuspid annular area, TAP = tricuspid annular perimeter, TAFAC = tricuspid annular fractional area change, TAFS = tricuspid annular fractional shortening.
*$p < 0.05$ vs. Controls, †<0.07 vs. Controls.

NT-proBNP and with poor prognosis [16]. The results of the present study could widen our knowledge demonstrating that enlarged TA is associated with its reduced function. These types of abnormalities are present in both AL-CA and TTR-CA. Although relatively small number of CA patients were compared, TTR-CA patients had somewhat larger TA dimensions with somewhat beneficial TA functional parameters as compared to those of AL-CA patients.

The above mentioned TA abnormalities could be theoretically due to direct infiltration and deposition of cardiac walls and valves including their annulus with amyloid fibrils. CA-associated ventricular and atrial dilation and dysfunction even on the right side could also have effects. The role of ageing, diabetes mellitus, hypertension, hypercholesterolaemia and higher grade valvular regurgitations cannot be excluded either.

Limitation section. The most important limitations are listed below:

- Unfortunately, image quality of 2D echocardiography and 3DSTE is not the same: worse image quality of 3DSTE could affect the results theoretically [6,7].
- There is subjectivity in selecting the plane of measurement which could be considered as an important limitation.
- 3D shape of the TA was not considered during assessments, only its 2D projection.
- Small number of CA patients were involved into the study. However, CA is a rare disorder, which explains involvement of relatively few patients in the present study during a 6-year period.
- Most CA patients had cardiovascular risk factors, which could also affect the results.
- 3DSTE-derived assessment of volumetric, strain and rotational parameters of cardiac chambers was not aimed to be performed.

Conclusions. Dilated TA is associated with its functional deterioration in CA.

CRediT authorship contribution statement

Attila Nemes: Conceptualization, Writing – original draft, Writing – review & editing. **Gergely Rácz:** Methodology, Investigation, Data curation. **Árpád Kormányos:** Methodology, Software, Investigation, Data curation, Writing – review & editing. **Dóra Földeák:** Investigation, Data curation, Resources. **Zita Borbényi:** Resources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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