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RESEARCH ARTICLE

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Cardiac amyloidosis is associated with increased aortic stiffness

Attila Nemes MD, PhD, DSc, FESC[1] | Dóra Földeák MD[2] | Péter Domsik MD, PhD[1] | Anita Kalapos MD, PhD[1] | Árpád Kormányos MD[1] | Zita Borbényi MD PhD[2] | Tamás Forster MD, PhD, DSc, FESC, FACC[1]

[1]2nd Department of Medicine and Cardiology Centre, Medical Faculty, Albert Szent-Györgyi Clinical Center, University of Szeged, Szeged, Hungary

[2]Division of Haematology, 2nd Department of Medicine and Cardiology Centre, Medical Faculty, Albert Szent-Györgyi Clinical Center, University of Szeged, Szeged, Hungary

Correspondence
Attila Nemes, 2nd Department of Medicine and Cardiology Center, Medical Faculty, Albert Szent-Györgyi Clinical Center, University of Szeged, H-6725 Szeged, P.O. Box 427, Semmelweis street 8, Hungary.
Email: nemes.attila@med.u-szeged.hu

Abstract

Objective: Cardiac amyloidosis (CA) is as an infiltrative disorder primarily caused by extracellular tissue deposition of amyloid fibrils in the myocardial interstitium. The current study was designed to test whether alterations in ascending aortic elastic properties could be detected by echocardiography in CA patients, and to compare their results to controls.

Patients and methods: We included 19 CA patients from which CA proved to be AL amyloidosis in 17 cases and transthyretin (TTR) amyloidosis in 2 cases. Their results were compared to 20 age-, gender-, and risk factor-matched controls.

Results: There was significantly greater interventricular septum and left ventricular (LV) posterior wall thickness, lower LV ejection fraction and greater *E/A* in CA patients than in controls, suggesting systolic, and diastolic dysfunction. CA patients also showed significantly reduced aortic strain and pulsatile change in aortic diameter, and increased aortic stiffness index.

Conclusion: These results suggest increased aortic stiffness in CA patients.

KEYWORDS
aortic, arterial wall stiffness, cardiac amyloidosis, echocardiography

1 | INTRODUCTION

Cardiac amyloidosis (CA) has been defined as an infiltrative disorder primarily caused by extracellular tissue deposition of amyloid fibrils in the myocardial interstitium. There are many types of CA depending on the precursors that may affect the heart.[1,2] Some forms of hereditary transthyretin-related (TTR) amyloidosis affect the heart almost invariably, whereas cardiac involvement in light chain amyloidosis (AL) is present in about 50% of the cases.[1,2] Amyloid involvement of the aorta is exceedingly rare.[3] Theoretically, the aortic wall could be subclinically infiltrated in CA leading to its stiffening and, consequentially, affecting left ventricular (LV) function due to altered Windkessel function and arterial-ventricular coupling.[4] Moreover, increased arterial stiffness have been proposed as one of the potential pathways through which associated disorders could lead to further cardiovascular abnormalities. This study was designed to test whether alterations in ascending aortic elastic properties could be detected by echocardiography in CA patients, and to compare their results to age-, gender-, and risk factor-matched controls.

2 | PATIENTS AND METHODS

2.1 | Patient population

The present study included 19 CA patients in whom CA proved to be AL amyloidosis in 17 cases and transthyretin (TTR) amyloidosis in 2 cases. All CA patients were alive and have been involved into this study at our tertiary center. Biopsy was performed in all cases to confirm the diagnosis of CA. The first positive biopsy site was the myocardium in 2 TTR-CA and in 3 AL-CA subjects. In the remaining AL-CA cases, kidney was the first positive biopsy site in 5 cases, gastrointestinal tract in 4 cases, skin and subcutaneous tissue in 4 cases, bone marrow in 3 cases,

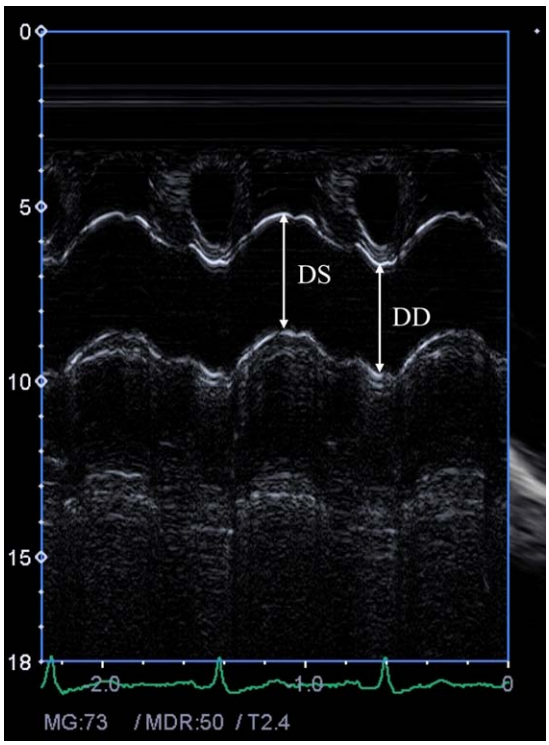

FIGURE 1 Measurement of systolic (DS) and diastolic (DD) diameters of the ascending aorta are shown on the M-mode tracing obtained at a level 3 cm above the aortic valve at parasternal long-axis view

and salivary gland in 1 case (there were 2 confirmation sites in 3 patients). Routine echocardiographic examination was performed in all cases, including measurement of wall thickness, and CA was defined in accordance with the current *consensus criteria* and practices.[5,6] Results from CA patients were compared to those of 20 age-, gender-, and risk factor-matched controls. None of the CA patients or control subjects consumed coffee or tea within 1 hour before combined echocardiographic and blood pressure (BP) measurements. Moreover, none of the CA patients or control subjects was smoker. The American Diabetes Association and World Health Organization *criteria* were used for definition of diabetes mellitus (DM). Hypertension was defined as either a systolic or a diastolic elevation of the BP (>140/90 mm Hg) or ongoing antihypertensive therapy. Hypercholesterolaemia was defined as total cholesterol level > 5.0 mmol/L or current treatment with lipid-lowering medications. Blood urea nitrogen and creatinine levels were determined to characterize renal function in CA patients. Each patient gave informed consent. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a prior approval by the human research committee of the University of Szeged.

2.2 | Two-dimensional echocardiography

Complete two-dimensional (2D) transthoracic Doppler echocardiography was performed in all cases using a Toshiba Artida echocardiography equipment (Toshiba, Tokyo, Japan) with a PST-30SBP (1–5 MHz) phased array transducer in the left lateral decubitus position from multiple windows. All echocardiographic studies were digitally stored and evaluated by a single expert (AN) who was blinded to the clinical data. All echocardiographic measurements were averaged from 3 beats. Modified Simpson's method was used for LV quantifications.[7]

2.3 | Measurement of echocardiographic aortic elastic properties

Aortic elasticity parameters were calculated following a validated method.[8,9] During a routine echocardiographic examination in parasternal long-axis view, an M-mode image was created at a level of 3 cm above the aortic valve, and systolic and diastolic ascending aortic diameters (SD and DD, respectively) were measured (Figure 1). The American Society of Echocardiography convention as the most accepted border definition criterion was used in measuring the leading edge of each layer. The SD and DD were measured at the time of maximum aortic anterior motion and at the peak of the QRS complex, respectively. At the same time, systolic (SBP) and diastolic (DBP) BP values were measured in supine position using an automatic cuff mercury sphygmomanometer on the left arm after 10 minutes of rest.

The following aortic elasticity parameters have been calculated:

- Pulsatile change in aortic diameter (mm) = SD − DD
- Aortic strain (AS) = (SD − DD)/DD
- Aortic stiffness index (ASI) = ln (SBP/DBP)/[(SD − DD)/DD], where "ln" is the natural logarithm
- Aortic distensibility (AD) = 2 × (SD − DD)/[(SBP − DBP) × DD]

2.4 | Statistical analysis

All data are presented as mean ± standard deviation. A value of $P < .05$ was considered to be statistically significant. Independent samples Student *t* test were used to compare continuous variables, and chi-square test and Fisher's exact test to compare categorical data. Numerical correlations were established by a Pearson correlation. MedCalc software was used for statistical calculations (MedCalc, Mariakerke, Belgium).

3 | RESULTS

3.1 | Clinical characteristics

Blood urea nitrogen and creatinine levels were 10.7 ± 9.4 mmol/L (3.1–43.9) and 119.1 ± 107 μmol/L (44–533), respectively, in CA patients, demonstrating 3 cases with mild-moderate and 2 cases with severe renal insufficiency. Clinical data, cardiovascular risk factors, and medications of CA patients and controls are presented in Table 1. Although none of the classic cardiovascular risk factors differed significantly between the groups, control subjects showed higher body mass index (BMI) and SBP and DBP values at the time of echocardiographic examinations.

3.2 | 2D echocardiographic data

Standard 2D echocardiographic data are summarized in Table 2. No wall motion abnormalities were found in any CA patients or healthy

TABLE 1 Clinical characteristics of patients with cardiac amyloidosis (CA) and controls

	CA patients (n = 19)	Controls (n = 20)	P
Clinical data			
Age (yr)	63.7 ± 9.1	59.3 ± 4.1	.06
Male gender (%)	14 (74)	17 (85)	.44
Height (m)	170.7 ± 7.7	162.6 ± 6.0	.001
Weight (kg)	76.1 ± 15.3	89.2 ± 17.7	.03
Body mass index (kg/m^2)	26.1 ± 5.0	33.5 ± 5.6	.0003
Diabetes mellitus (%)	2 (11)	3 (15)	1.00
Hypertension (%)	12 (67)	15 (75)	.50
Hypercholesterolaemia (%)	6 (32)	8 (40)	.74
Blood pressure values			
Systolic blood pressure (mm Hg)	104.3 ± 12.9	145.6 ± 11.9	<.0001
Diastolic blood pressure (mm Hg)	69.1 ± 10.6	89.1 ± 9.2	<.0001
Aortic pulse pressure (mm Hg)	35.3 ± 10.6	60.0 ± 10.8	<.0001
Main medications			
β-blockers (%)	8 (42)	5 (25)	.32
ACE-inhibitors (%)	10 (53)	9 (45)	.75
Diuretics (%)	13 (68)	0 (0)	.0001

Abbreviation: ACE, angiotensin-converting enzyme.

subjects. Significant (≥ grade 3) mitral regurgitation could not be detected in any of the CA patients or control subjects. Significantly thickened interventricular septum and LV posterior wall, reduced LV ejection fraction, and increased *E/A*, suggesting systolic and diastolic dysfunction could be detected in CA patients (Table 2).

3.3 | Echocardiographic aortic elastic properties

Significantly reduced aortic strain and pulsatile change in aortic diameter and increased aortic stiffness index could be demonstrated in CA patients as compared to matched controls (Table 2). From CA patients, 10 were in NYHA I, 3 in NYHA II, 3 in NYHA III, and 3 in NYHA IV functional classes. The average ASI differed significantly between CA patients in NYHA classes III-IV and CA patients in classes NYHA I-II (20.40 ± 14.80 vs 9.05 ± 8.84, $P = .03$). None of other LV and aortic variables showed difference between CA patients in different functional classes.

3.4 | Correlations

Significant correlations could be detected between ASI and LV end-diastolic diameter ($r = .45$, $P = .05$), posterior wall thickness ($r = .49$, $P = .03$), and interventricular septum thickness ($r = .46$, $P = .05$) in CA patients. None of other aortic data correlated with any LV variable in CA patients and in controls.

4 | DISCUSSION

CA is caused by extracellular deposition of abnormal amyloid fibrils within the heart with infiltration occurring in all anatomical structures.[10] To the best of the authors' knowledge, this is the first echocardiographic demonstration of alterations in aortic elastic properties in CA patients. Most of our CA cases showed AL amyloidosis, where AL fibrils are derived from monoclonal immunoglobulin light chains with typical multi-organ infiltration.[11] In spite of the progress made over the past decades in therapy, AL cardiomyopathy remains associated with poor survival.[10] There are several cardiac complications of myocardial amyloid fibril deposition, the most important being severe congestive heart failure, atrial fibrillation, ventricular arrhythmias, conduction abnormalities, orthostatic hypotensive episodes, and autonomic dysfunction.[2] In 2 cases, TTR amyloidosis was found, where typical cardiac manifestations are arrhythmias, syncope or sudden cardiac death, dyspnoea, and heart failure due to restrictive cardiomyopathy.[6]

The main finding of the present study was increased ASI and reduced AS and pulsatile change in aortic diameter in CA patients as compared to controls. The main cardiovascular risk factors (age, male

TABLE 2 Two-dimensional echocardiographic data of patients with cardiac amyloidosis (CA) and that of controls

	CA patients (n = 19)	Controls (n = 20)	P
Two-dimensional echocardiography			
Left atrial diameter (mm)	46.3 ± 7.2	40.2 ± 10.2	.10
Left ventricular end-diastolic diameter (mm)	47.0 ± 5.2	46.2 ± 3.8	.58
Left ventricular end-systolic diameter (mm)	30.7 ± 5.2	28.9 ± 3.9	.26
Interventricular septum (mm)	15.1 ± 3.4	9.9 ± 1.1	<.0001
Left ventricular posterior wall (mm)	14.2 ± 2.4	9.7 ± 1.0	<.0001
Left ventricular ejection fraction (%)	59.3 ± 11.7	66.2 ± 6.7	.03
Mitral annular plane systolic excursion (mm)	12.5 ± 4.4	20.2 ± 3.5	.01
Systolic aortic diameter (mm)	30.6 ± 4.0	29.8 ± 3.7	.56
Diastolic aortic diameter (mm)	29.1 ± 3.7	27.6 ± 3.2	.22
E/A	1.89 ± 1.15	0.88 ± 0.21	.0007
Aortic elastic properties			
Pulsatile change in aortic diameter (mm)	1.53 ± 1.08	2.22 ± 1.04	.05
Aortic strain (AS)	0.054 ± 0.039	0.080 ± 0.036	.04
Aortic distensibility (AD) (cm^2/dynes 10^{-6})	2.42 ± 1.49	2.13 ± 0.88	.47
Aortic stiffness index (ASI)	12.6 ± 10.7	7.5 ± 3.6	.05

gender, DM, hypertension, and hypercholesterolaemia) were similar between the groups. Although actual BP values at echocardiographic measurements were higher in controls, aortic elastic properties appeared significantly impaired in CA patients. Age and BMI were found to be predictors of increased aortic stiffness in a recent study,[12] but BMI was higher in our controls than in our patients with CA.

Several factors could play a role in increased aortic stiffness in CA. Regarding the literature, amyloid involvement of the aorta is exceedingly rare.[3] However, theoretically together with myocardial tissue, aortic wall could be infiltrated latently by amyloid fibrils leading to endothelial dysfunction and impairment of its Windkessel function. Most CA patients had one or more classic cardiovascular risk factors (higher age, male gender, hypertension, DM, or hypercholesterolaemia) which could also have an effect on arterial stiffness.[13] Moreover, ventricular-arterial coupling and systolic and diastolic LV dysfunction should also be considered when interpreting these findings.[14] CA patients had significantly higher aortic stiffness in higher NYHA functional classes, suggesting an important role of aortic stiffness in the development of heart failure in these cases. The clinical importance of the present study is to draw attention on increased aortic stiffness and associated reduced functional capacity in CA patients. However, further clinical studies are warranted to assess the effects of improvement of vascular elasticity in these cases. Theoretically, all medical treatments confirmed to improve vascular function and/or heart failure should be considered in CA patients. Our CA patients were treated well with β-blockers and ACE-inhibitors, which are known to have positive effects on arterial stiffness over heart failure.[15,16]

5 | LIMITATIONS OF THE STUDY

The main limitations of this study are:

- A mixed population of CA patients was examined including both TTR and AL cases.
- BP measured in the brachial artery may be different from that in the ascending aorta (central pressure) due to pulse pressure (PP) amplification toward the periphery. PP amplification depends on the pulse wave propagation velocity, which itself is positively but nonlinearly related to BP. Moreover, gender, age, and body composition have a significant impact on PP amplification.[17] However, echocardiography-derived aortic stiffness data correlate well with those obtained by invasive methods.[8]
- Controls had higher BP values and PP than CA patients, suggesting better controlled BP in CA patients. This could strengthen our findings since although BP and PP were higher in controls, aortic stiffness was greater in CA patients.
- Measurement of aortic diameter data in systole and diastole was performed only in one plane. However, it should be considered that large vessels exhibit nonlinear variations of circumferential stress and tangent elastic moduli even within the normal pressure range.[18] Therefore, aortic elastic properties could theoretically be dissimilar at different segments of the aorta.

6 | CONCLUSION

Results of the present study suggest increased aortic stiffness in CA patients than in age-, gender-, and risk factor-matched controls.

CONFLICT OF INTEREST

None declared.

ORCID

Attila Nemes MD, PhD, FESC http://orcid.org/0000-0002-7570-6214

REFERENCES

[1] Falk RH. Diagnosis and management of the cardiac amyloidoses. *Circulation*. 2005;112:2047–2060.

[2] Mohty D, Damy T, Cosnay P, et al. Cardiac Amyloidosis: updates in diagnosis and management. *Arch Cardivasc Dis*. 2013;106:528–540.

[3] Gašparović H, Petričević M, Đurić E, Brida V, Jelašić D, Biočina B. Amyloidosis of the aortic root in a patient with polyarteritis nodosa. *Coll Antropol*. 2014;38:1051–1053.

[4] Belz GG. Elastic properties and Windkessel function of the human aorta. *Cardiovasc Drugs Ther*. 1995;9:73–83.

[5] Gertz MA, Comenzo R, Falk RH, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18–22 April 2004. *Am J Hematol*. 2005;79:319–328.

[6] Rapezzi C, Merlini G, Quarta CC. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. *Circulation*. 2009;120:1203–1212.

[7] Nemes A, Forster T. Recent echocardiographic examination of the left ventricle – from M-mode to 3D speckle-tracking imaging. *Orv Hetil*. 2015;156:1723–1740.

[8] Stefanadis C, Stratos C, Boudoulas H, Kourouklis C, Toutouzas P. Distensibility of the ascending aorta: comparison of invasive and non-invasive techniques in healthy men and in men with coronary artery disease. *Eur Heart J*. 1990;11:990–996.

[9] Nemes A, Geleijnse ML, Forster T, Soliman OII, Ten Cate FJ, Csanády M. Echocardiographic evaluation and clinical implications of aortic stiffness and coronary flow reserve and their relation. *Clin Cardiol*. 2008;31:304–309.

[10] Guan J, Mishra S, Falk RH, Liao R. Current perspectives on cardiac amyloidosis. *Am J Physiol Heart Circ Physiol*. 2012;302:H544–H552.

[11] Estep JD, Bhimaraj A, Cordero-Reyer AM, Bruckner B, Loebe M, Torre-Amione G. Heart transplantation and end-stage cardiac amyloidosis: a review and approach to evaluation and management. *Methodist Debakey Cardiovasc J*. 2012;8:8–16.

[12] Nemes A, Gavallér H, Csajbók É, Forster T, Csanády M. Obesity is associated with aortic enlargement and increased stiffness: an echocardiographic study. *Int J Cardiovasc Imaging*. 2008;24:165–171.

[13] Breithaupt-Grögler K, Belz GG. Epidemiology of the arterial stiffness. *Pathol Biol (Paris)*. 1999;47:604–613.

[14] Saba PS, Cameli M, Casalnuovo G, et al. Ventricular-vascular coupling in hypertension: methodological considerations and clinical implications. *J Cardiovasc Med (Hagerstown)*. 2014;15:773–787.

[15] Niu W, Qi Y. A meta-analysis of randomized controlled trials assessing the impact of beta-blockers on arterial stiffness, peripheral blood pressure and heart rate. *Int J Cardiol*. 2016;218:109–117.

[16] Janić M, Lunder M, Sabovič M. Arterial stiffness and cardiovascular therapy. *Biomed Res Int*. 2014;2014:621437.

[17] Pichler G, Martinez F, Vicente A, Solaz E, Calaforra O, Redon J. Pulse pressure amplification and its determinants. *Blood Press*. 2016; 25:21–27.

[18] Kamenskiy AV, Dzenis YA, MacTaggart JN, Lynch TG, Jaffar Kazmi SA, Pipinos II. Nonlinear mechanical behavior of the human common, external, and internal carotid arteries in vivo. *J Surg Res*. 2012;176:329–336.

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