Echocardiographic and Biohumoral Characteristics in Patients With AL and TTR Amyloidosis at Diagnosis

Address for correspondence:
Francesco Cappelli, MD,
Intensive Cardiac Care Unit,
Department of Heart and Vessels,
University of Florence and Azienda
Ospedaliero–Universitaria Careggi,
Largo Brambilla 3,
50134 Florence,
Italy,
cappellifrancesco@inwind.it

Francesco Cappelli, MD; Samuele Baldasseroni, MD; Franco Bergesio, MD; Stefano Perlini, MD; Francesco Salinaro, MD; Luigi Padeletti, MD; Paola Attanà, MD; Alessandro Paoletti Perini, MD; Alberto Moggi Pignone, MD; Elisa Grifoni, MD; Alessia Fabbri, MD; Niccolò Marchionni, MD; Gian Franco Gensini, MD; Federico Perfetto, MD

Intensive Cardiac Care Unit, Heart and Vessel Department (Cappelli, Baldasseroni), University Hospital Careggi, Florence, Italy; Tuscan Regional Amyloid Center (Cappelli, Bergesio, Perfetto), University Hospital Careggi, Florence, Italy; Department of Internal Medicine and Amyloidosis Research and Treatment Center (Perlini, Salinaro), Fondazione IRCCS Policlinico San Matteo and University of Pavia, Pavia, Italy; Department of Heart and Vessels (Padeletti, Attanà, Paoletti Perini, Gensini), University of Florence, Florence, Italy; Department of Clinical and Experimental Medicine (Pignone, Grifoni, Fabbri), University of Florence, Florence, Italy; Department of Clinical and Experimental Medicine (Marchionni), University of Florence, Florence, Italy

ABSTRACT

Background: Few studies have analyzed the clinical and echocardiographic differences between light-chain (AL) and transthyretin (TTR) amyloidosis.

Hypothesis: The aim of the present research was to compare, in a real-world setting, the clinical and echocardiographic profiles of these kinds of amyloidosis, at the time of diagnosis, using new-generation echocardiography.

Methods: Seventy-nine patients with AL and 48 patients with TTR amyloidosis were studied.

Results: According to the criterion of mean left ventricular (LV) thickness >12 mm, 45 AL (C-AL) and all TTR patients had cardiac amyloidotic involvement, whereas 34 AL patients did not. TTR patients had increased right ventricular (RV) and LV chambers with increased RV and LV wall thickness and reduced LV ejection fraction and fractional shortening. Furthermore, TTR patients showed lower N-terminal pro Brain Natriuretic Peptide concentrations and New York Heart Association functional class when compared with C-AL.

Conclusions: Our data show that at time of first diagnosis, TTR patients have a more advanced amyloidotic involvement of the heart, despite less severe symptoms and biohumoral signs of heart failure. We can hypothesize that we observed different diseases at different stages. In fact, AL amyloidosis is a multiorgan disease with quick progression rate, that becomes rapidly symptomatic, whereas TTR amyloidosis might have a slow progression rate and might remain poorly symptomatic for a greater amount of time.

Introduction

Systemic amyloidoses are rare diseases characterized by extracellular deposition of protein-derived fibrils in various tissues and organs, including the heart.[1,2] Amyloidosis classification is based on the protein composition of the fibrils and on its clinical features. Among this wide and diversified spectrum, the 2 most frequent and clinically challenging etiologies are the immunoglobulin light-chain (AL) form, and transthyretin-related (ATTR) form. The ATTR form can be further classified in hereditary transthyretin-related amyloidosis (ATTRm), due to mutations in the gene codifying for transthyretin, and systemic senile amyloidosis, a noninherited form caused by the deposition of the wild-type transthyretin (TTR) protein (ATTRwt) in the extracellular space.[2] Cardiac involvement is frequent in both AL and ATTR amyloidosis, and is associated with important clinical and psychological consequences[3,4] that have a significant impact on prognosis.[5]

In recent years, authors have focused their attention on the cardiac involvement of the AL form, assessing, by means of echocardiography, both left ventricular (LV) and right ventricular (RV) dysfunction and their consequences on prognosis.[6–11] On the other hand, less attention has been paid to LV and RV involvement and dysfunction in patients affected by TTR amyloidosis. This discrepancy might be due to the low incidence of the disease in nonendemic areas, to the wide variability of the clinical spectrum associated with different genetic mutations, and to the geographical

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Received: July 19, 2014
Accepted with revision: October 3, 2014

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22353

distribution of this form.[12] On the other hand, ATTRwt-induced heart failure (HF) in the elderly is likely to be both an underdiagnosed and misdiagnosed clinical entity.

Furthermore, clinical research has been mainly limited to patients with ATTRm with single mutation,[13–15] and only 1 study performed a comprehensive phenotypic evaluation of different ATTRm mutations in a wide area.[16]

Despite the wide clinical heterogeneity between AL- and TTR-related forms, only a few studies, based on small populations, analyzed the clinical and echocardiographic differences between AL and TTR amyloidosis.[17–19] Ng et al, comparing patients affected by either ATTRwt or AL amyloidosis matched for HF New York Heart Association (NYHA) functional class, showed that the former group had thicker LV walls despite comparable LV systolic and diastolic function, at least when assessed by the traditional echocardiographic evaluation.[18] On the other hand, Ogiwara and coauthors demonstrated that, when matched for LV wall thickness, ATTRm patients presented less-impaired LV longitudinal systolic function as assessed by tissue Doppler imaging (TDI)-derived strain, when compared with patients affected by AL amyloidosis.[19]

A single, multicenter, longitudinal study[5] compared, at the time of first diagnosis, the structural and functional characteristics of a large group of patients with AL or TTR-related cardiac amyloidosis, based on traditional echocardiography evaluation and, consequently, without any insight on myocardial deformation and strain analysis. All these studies were focused mainly on LV structure and systo-diastolic function, with scarce attention to the involvement of the right ventricle.

Recently, TDI and 2-dimensional speckle-tracking echocardiography have enabled clinicians and researchers to perform a more careful and accurate evaluation of the systolic and diastolic function of both ventricles. For these reasons, we performed the present single-center investigation, aiming at comparing in a real-world setting, the clinical and echocardiographic profiles of the 2 most common types of amyloidosis, at time of diagnosis, by means of the new generation of echocardiographic technologies.

Methods

Seventy-nine consecutive AL amyloidosis patients, diagnosed between March 2006 and August 2013 at the Regional Referral Centre for Amyloidosis (Florence, Italy) were compared with 48 consecutive ATTR amyloidosis patients diagnosed over the same lapse of time in the same center. All participants gave their informed written consent according to the Helsinki declaration.

Diagnosis of AL amyloidosis was made by means of biopsy of an involved organ, demonstrating the typical Congo red birefringence when viewed under polarized light. Sites of positive biopsy were abdominal fat in 56 patients (70%), kidneys in 14 (18%), salivary glands in 7 (9%) and the myocardium in 2 (3%). All positive biopsies showed the typical Congo red birefringence under polarized light. AL amyloidosis was confirmed by the finding of either a monoclonal protein in patients' serum or urine, or a monoclonal population of plasma cells in the bone marrow, after immunohistochemistry evaluation, in the absence of any TTR mutation at DNA analysis. In 2 cases of sole myocardial involvement, electron microscopy with immunogold labeling was necessary to unambiguously characterize the nature of the amyloid fibrils.

The diagnosis of ATTRm amyloidosis was based on the biopsy of abdominal fat in 10 patients (52%), of the myocardium in 6 (32%), of salivary glands in 3 (16%), and, since 2009, by positive 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD) scintigraphy (15 patients). Genotype data were available for all 19 patients with ATTRm; mutations were Ile68Leu (n = 11 patients, 62%), Val122Ile (n = 5 patients, 28%), Glu54Val (n = 1 patient), Gly57Arg (n = 1 patient), and Phe64Leu (n = 1 patient). All 15 patients who underwent 99mTc-DPD scintigraphy showed the characteristic increase in the myocardial uptake of the bone tracer, further confirming the diagnosis of TTR-related cardiac amyloidosis.[16]

Finally, the diagnosis of ATTRwt amyloidosis (29 patients) was made by tissue biopsy or by positive 99mTc-DPD scintigraphy, in the absence of TTR mutation and of plasma cells dyscrasia. A total of 19 patients (66%) had histological proof of ATTR amyloidosis by Congo red and immunohistochemical staining of the myocardium (n = 6, 31%) or other tissues (n = 13, 69%, abdominal fat in 6 patients, carpal tunnel biopsy in 4, and salivary glands in 3). In 10 (34%) patients affected by definite TTRwt despite negative tissue biopsy, cardiac amyloidosis was defined as intense 99mTc-DPD uptake in the heart (grade 2 or 3, as defined by Perugini et al[20]) in the absence of a plasma cell dyscrasia and of TTR mutation; in the last group of patients, cardiac magnetic resonance imaging was performed and showed the presence of late gadolinium enhancement, which is consistent with the amyloid involvement of the myocardium.

All participants underwent a thorough clinical evaluation at the entry visit. In addition, the concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured by an electrochemiluminescence sandwich immunoassay (Roche Diagnostics, Indianapolis, IN) in the central hospital laboratory, whereas troponin I was analyzed by an immunochemiluminescence assay, using a Centaur XP system (Siemens Healthcare, Erlangen, Germany). Creatinine clearance was estimated by the Modification of Diet in Renal Disease (MDRD) formula.[21] Both systolic and diastolic arterial blood pressure were recorded.

A criterion of exclusion from the study was the presence of any comorbidity that might have caused the increase of LV wall thickness, such as long-standing arterial hypertension or moderate-to-severe aortic valve stenosis.

Patients were classified as affected by echocardiography detectable cardiac AL amyloidosis if the mean value of LV wall thickness (half of the sum of LV septum and posterior wall thickness) was >12 mm, and as not having cardiac involvement if this criterion was not satisfied.[22] As there is currently no published consensus for ATTR amyloidosis, the same echocardiographic criteria were used for these patients.

Standard and TDI Echocardiography

At the time of diagnosis, patients were referred to our echo lab for a complete evaluation, including M-mode,

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22353

2-dimensional, conventional, tissue Doppler, and speckle strain echocardiography. All the exams were performed by a single experienced operator (F.C.), who was blinded to patients' clinical history, using a Vivid 7 System (Vingmed; General Electric, Horten, Norway) equipped with a 3S probe. At least 3 consecutive beats were recorded, and images were digitized and analyzed off-line. According to the standards of the American Society of Echocardiography,[23] the following parameters were assessed: end-diastolic thickness of both ventricular septum (IVS) and LV posterior wall (PW), LV end-diastolic and end-systolic diameters (LVEDD and LVESD, respectively), body surface area (BSA), indexed LV mass ($LVmass_{ind}$), LV endocardial fractional shortening (FS), left atrial area (LA area, evaluated from the apical 4-chamber view at the end of systole), LV end-diastolic volume and LV end-systolic volume (LVESV), ejection fraction (EF, estimated with the biplane Simpson method), mitral peak flow velocity in early and late diastole (E and A, respectively, during atrial contraction), E wave Deceleration Time (DT), E/A ratio, ejection time of the aortic valve and of the pulmonary valve, LV and RV myocardial performance index (MPI)—defined as the sum of isovolumic contraction and relaxation times divided by the ejection time, as previously described [24]—RV free wall thickness (RVFW), RV end-diastolic diameter (RVEDD, evaluated from the parasternal long-axis view), and the systolic displacement of the lateral portion of the tricuspid annular plane (TAPSE). LV mass indexed to BSA was calculated using a previously described formula for hypertensive patients LVmass: $0.8 \times 1.04 \times (\text{LVEDD} + \text{IVST} + \text{LVPWT})^3 - \text{LVEDD}^3) + 0.6)/\text{BSA}$.[25]

Pulmonary artery systolic pressure (PASP) was approximated by adding to the transtricuspid pressure gradient an estimate of right atrial pressure. We also evaluated pulsed TDI-derived early diastolic peak velocity at lateral mitral annulus (E′), as an index of LV relaxation, and E/E′ ratio, as index of LV filling pressure. Transtricuspid peak flow velocity in early and late diastole (E tricuspid and A tricuspid, respectively) and their ratio were also measured. Lateral tricuspid annulus pulsed TDI-derived early diastolic and systolic peak velocities (E′, S′ respectively), and the E/E′ ratio, as an index of the RV filling pressure, were also assessed.

By means of 2-dimensional speckle tracking echocardiography, LV longitudinal peak systolic strain (LV long strain), expressed as the average of the 3apical views, and RV (RV long strain) longitudinal peak systolic strain, expressed as the average of measurement of the 3 free wall segments in the apical 4-chamber view, were evaluated.

Statistical Analysis

Statistical analysis was conducted using the SPSS for Windows package version 13 (SPSS Inc., Chicago, IL). Categorical and continuous variables were expressed as frequencies (percentages) and as mean ± standard deviation, respectively. Categorical comparisons were performed by means of the Pearson χ^2 test, whereas the 1-factor analysis of variance (ANOVA) was used for comparisons between groups. Post hoc analyses were performed using the Scheffe method. A 2-tailed P value <0.05 was considered statistically significant.

Interobserver variability was assessed for LV long strain, RV long strain, mitral annulus E′ and tricuspid annulus E′ and S′, in 20 randomly selected patients, and calculated as the standard deviation of the differences between the measurements of 2 independent observers who were unaware of any other patient's data; this variability was expressed as percentage of the average value.

Results

The population of the study included 79 patients with systemic AL amyloidosis and 48 patients with TTR-related amyloidosis. According to international criteria, 45 AL patients (57%) had cardiac amyloidosis (C-AL group), whereas the other 34 did not have echocardiographic evidence of cardiac involvement (NC-AL group). Among patients with TTR-related amyloidosis, 29 had ATTRwt. All mutations presented a main cardiac phenotype, and in all cases but 2 (1 patient with glu54val and 1 patient with phe64leu), the diagnostic route was cardiologic.

Two patients, 1 with ATTRwt and 1 with ATTRm, had an incidental diagnosis, due to the unexpected 99mTc-DPD myocardial uptake at a scintigraphic examination performed as part of the oncologic follow-up of prostatic neoplasm. All patients with TTR-related amyloidosis presented echocardiographic evidence of cardiac involvement at diagnosis. Clinical and biohumoral characteristics were reassumed in Table 1.

Left Ventricular Dimension and Function

The results of the ANOVA analysis are summarized in Table 2. TTR patients showed a significant increase in LVESD and LVESV, associated to the reduction of EF. A progressive increase in IVS and PW thickness, $LVmass_{ind}$, and LA area was observed between groups, with lower mean values in NC-AL patients, and higher mean values in the ATTR group. FS was significantly reduced in TTR patients, compared to other groups. LV MPI and LV longitudinal strain were significantly impaired in both C-AL and TTR groups.

As to the evaluation of the diastolic function, both C-AL and TTR patients showed reduced A and E′ values, with increase in the E/E′ ratio, compared to the NC-AL group. Moreover, a progressive increase in the E/A ratio was observed in the 3 groups, the mean values being significantly lower in NC-AL patients and higher in TTR patients.

RV Dimension and Function

As reported in Table 3, RVEDD was significantly increased in TTR patients, whereas a progressive increase in RVFW was evidenced between groups, mean values being significantly lower in NC-AL patients and higher in TTR patients. No difference was observed across groups at traditional Doppler diastolic evaluation, whereas at tricuspid annulus TDI analysis, TTR and C-AL subjects showed significantly lower E′ values with increased E/E′ ratios. RV systolic function was significantly impaired in TTR and C-AL patients at traditional, TDI and 2-dimensional speckle tracking evaluation (TAPSE, S′, and RV longitudinal strain, respectively). RV MPI was significantly reduced in TTR

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22353

Table 1. Demographic, Clinical, and Biohumoral Characteristics of the Studied Population

	NC-AL, N = 34	C-AL, N = 45	TTR, N = 48	*P*
Age, y	69.4 ± 10.4	68.2 ± 10.2	75.8 ± 9.7[a]	<0.001
Gender, M/F	21 (62%)/13 (38%)	23 (51%)/22 (49%)	40 (83%)/8 (17%)	<0.0001
BSA, m^2	1.7 ± 0.16	1.7 ± 0.14	1.8 ± 0.14	<0.20
GFR, mL/min	60.4 ± 32.5	59.9 ± 22.8	67.6 ± 24.6	<0.38
NT-proBNP, ng/L	568 ± 919[b]	8329 ± 10342	4497 ± 4852[a]	<0.0001
Troponin, ng/L	0.03 ± 0.03[b]	0.19 ± 0.25	0.16 ± 0.14	<0.004
ASBP, mm Hg	130.4 ± 26.9[c]	112.5 ± 18.0	120.6 ± 25.4	<0.01
ADBP, mm Hg	74.6 ± 10.9[c]	67.5 ± 10.6	73.7 ± 11.9	<0.01
NYHA class				
I	34 (100%)	6 (13%)[d]	10 (21%)[e]	<0.0001
II	0	22(49%)	18(38%)	
III	0	11(25%)	20(41%)	
IV	0	6(13%)	0	

Abbreviations: ADBP, arterial diastolic blood pressure; ASBP, arterial systolic blood pressure; BSA, body surface area; C-AL, cardiac AL amyloidosis; GFR, glomerular filtration rate; NC-AL, noncardiac AL amyloidosis; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Associationn; TTR, transthyretin-related amyloidosis.
Scheffe's post hoc analysis:
[a]TTR vs others, $P < 0.05$. [b]NC-AL vs others, $P < 0.05$; [c]NC-AL vs C-AL, $P < 0.05$. χ^2 analysis: [d]C-AL vs NC-AL, $P < 0.0001$. [e]TTR vs C-AL, $P < 0.05$.

patients compared to NC-AL patients, whereas no significant difference was observed between the TTR and C-AL groups. A significant increase in PASP values was observed in both C-AL and TTR patients.

Reproducibility

The interobserver variability was 4% and 5% for mitral annulus E′ and E/E′, whereas it was 8% and 9% for tricuspidal annular S′ and E/E′, respectively. Regarding 2-dimensional speckle strain–derived analysis, the interobserver variability was 6% for LV longitudinal strain and 8% for RV longitudinal strain.

Discussion

Our study performed a thorough and technologically updated evaluation of RV-LV morphology and systolic and diastolic functions in patients affected by both TTR and AL amyloidosis.

According to the echocardiographic phenotype, we can characterize 2 different scenarios: in our series, at time of diagnosis, nearly half of AL patients do not present cardiac involvement, according to the echocardiographic international criteria. On the other hand, in our population, ATTR was diagnosed when cardiac involvement was already clearly evident at echocardiography in 100% of patients. A possible reason of this significant dichotomy might be the different diagnostic route to get to diagnosis. Although nearly the whole population of TTR patients followed a cardiological diagnostic route, in almost one-third of patients affected by AL amyloidosis, the diagnosis was pointed out after a hematological or a nephrological evaluation.

Apart from AL patients without echocardiographic involvement, the 2 groups with cardiac involvement (C-AL and TTR) presented a significantly different cardiac phenotype.

ATTR patients presented increased dimension of both LV and RV chambers with larger atrium and higher LV and RV wall thickness. Moreover, patients with ATTR showed impaired LV EF and FS, whereas patients with AL amyloidosis still had normal values. At diagnosis, both C-AL and ATTR patients presented a significant impairment of LV and RV systolic function assessed by speckle strain, with significant reduction in biventricular systolic longitudinal function. Furthermore, both C-AL and ATTR patients presented a significant and comparable impairment of both RV and LV diastolic function assessed by TDI echocardiography.

Despite the above-mentioned characteristics, it might appear somehow unexpected that, in comparison to C-AL patients, ATTR patients showed significantly less HF symptoms according to the NYHA functional class classification, and significantly reduced NT-proBNP plasma values.

Our data show that ATTR patients present at diagnosis a more advanced degree of amyloidotic heart involvement (in terms of wall thickness, which can be regarded as an approximation of the extent of amyloid deposition), but at the same time, less severe symptoms and biohumoral signs of HF.

According to our findings, it is clearly evident that 2 different relationships between HF symptoms and echocardiographic findings exist, based on the etiology of the disease. In ATTR amyloidosis, a manifest divergence between severity of HF symptoms and cardiac morphological involvement shows up. On the other hand,

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22353

Table 2. Left Ventricular Echocardiographic Characteristic of Studied Population

	NC-AL, N = 34	C-AL, N = 45	TTR, N = 48	P
LVEDD, mm	45.2 ± 4.3	44.9 ± 6.9	46.1 ± 5.7	<0.63
LVESD, mm	26.6 ± 4.8	29.3 ± 6.2	33.1 ± 6.7[a]	<0.0001
FS %	41.4 ± 7.2[b]	34.5 ± 9.1	28.5 ± 8.7[a]	<0.0001
IVS, mm	10.3 ± 0.9[b]	15.2 ± 2.6	17.4 ± 2.7[a]	<0.0001
LVPW, mm	10.3 ± 1.2[b]	15 ± 2.2	16.3 ± 2.1[a]	<0.0001
LV mass index, g/m²	97.1 ± 19.3[b]	163.3 ± 36.2	197.4 ± 49.6[a]	<0.0001
LA area, cm²	18.7 ± 3.7[b]	22.7 ± 3.8	26.6 ± 5[a]	<0.0001
LVEDV, mL	80.3 ± 18.6	81.1 ± 27.1	88.5 ± 24.5	<0.23
LVESV, mL	32.6 ± 12.5	34.9 ± 15.8	46.1 ± 20.7[a]	<0.001
EF %	59.6 ± 8.8	57.6 ± 9.2	49.1 ± 12.1[a]	<0.0001
LV long strain %	−16.8 ± 7.7[b]	−10 ± 4.2	−8.1 ± 3.7	<0.0001
Valve thickening, yes/no	4 (12%)/30 (88%)	22 (49%)/23 (51%)	29 (60%)/19 (40%)	<0.0001
Pericardial effusion, yes/no	1 (3%)/33 (97%)	13 (30%)/32 (70%)	12 (25%)/36 (75%)	<0.0001
Mitral regurgitation, mild–moderate/severe	32 (94%)/2 (6%)	35 (78%)/10 (22%)	39 (81%)/9 (19%)	<0.14
E, cm/s	70.4 ± 18.9	78.5 ± 20.2	80.9 ± 17.1[a]	<0.04
A, cm/s	85.2 ± 21.4[b]	58.6 ± 24.9	46.3 ± 22.7	<0.0001
E/A	0.84 ± 0.2[b]	1.62 ± 0.9	2.12 ± 1.0[a]	<0.0001
DT, ms	217.7 ± 68.5	195.1 ± 80	178.9 ± 66	<0.06
E′ cm/s	7.1 ± 1.9[b]	4.6 ± 1.3	4.6 ± 1.5	<0.0001
E/E′	9.9 ± 3.4[b]	18.1 ± 7.1	19.3 ± 6.5	<0.0001
AET, ms	289.2 ± 31.7[b]	253.8 ± 37.6	264.3 ± 35.3	<0.0001
LV MPI	0.36 ± 0.14[b]	0.52 ± 0.21	0.57 ± 0.21	<0.0001

Abbreviations: A, late diastolic mitral peak flow velocity; AET, aortic valve ejection time; C-AL, cardiac AL amyloidosis; DT, decelleration time; E, early diastolic mitral peak flow velocity; E′, early diastolic peak velocity at lateral mitral annulus; FS, fractional shortening; EF, ejection fraction; IVS, interventricular septum thickness; LA, left atrium; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVEDV, LV end-diastolic volume; LVESD, LV end-systolic diameter; LVESV, LV end-systolic volume; LV long strain, LV longitudinal 2-dimensional-speckle strain; LVPW, posterior wall thickness; MPI, myocardial performance index; NC-AL, noncardiac AL amyloidosis; TTR, transthyretin-related amyloidosis.
Scheffe's post hoc analysis:
[a]TTR vs others, $P < 0.05$. [b]NC-AL vs others, $P < 0.05$.

in the AL group, the severity of clinical symptoms increased directly with cardiac involvement.

In accordance with this hypothesis, it has already been demonstrated[5,18,19] that ATTRm and ATTRwt amyloidosis have better prognoses, despite patients' older age at diagnosis and echocardiographic evidence of thicker ventricles, with an overall survival at 2 years of 63% for AL, 98% for ATTRm, and 100% for ATTRwt.[3]

More recently, Quarta and colleagues confirmed the fact that prognosis reflects the etiology of the disease in a large series of patients including AL, ATTRm, and ATTRwt.[26] Moreover, these authors corroborated the utility of the use of longitudinal strain to characterize the differences in the cardiac involvement of the 3 forms of amyloidosis. Similar to our study, they found that AL patients showed lower wall thickness and LV mass despite worse prognostic outcome.

The worse clinical outcome of AL amyloidosis patients and the presence of more symptoms of HF together with higher NT-proBNP plasma levels, despite a lower degree of myocardial infiltration, might be related to the direct cardiotoxic effect of circulating light chains. Animal studies have shown that the infusion of amyloidogenic light chains into isolated mice hearts results in cardiac dysfunction, probably mediated by the increase in cellular oxidative stress.[27,28] Moreover, Migrino and colleagues demonstrated that brief exposure to physiological amounts of circulating light chain can induce endothelial dysfunction in human adipose and coronary arterioles, and increase the apoptotic injury in coronary artery endothelial cells, likely as a result of oxidative stress, reduced nitric oxide bioavailability, and production of peroxynitrite.[29]

Because of the cross-sectional design of our study, we can only speculate about the hypothesis that TTR amyloidosis

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22353

Table 3. Right Ventricular Echocardiographic Characteristic of Studied Population

	NC-AL, N = 34	C-AL, N = 45	TTR, N = 48	P
RVFW, mm	5.9 ± 1.4[a]	7.4 ± 1	8.7 ± 1.5[b]	<0.0001
RVEDD, mm	26.5 ± 5.9	28.8 ± 5.1	32.4 ± 6.3[b]	<0.0001
E tricuspid, cm/s	47.2 ± 10.2	47.5 ± 13.8	48.2 ± 13.9	<0.94
A tricuspid, cm/s	45.2 ± 12.1	44.7 ± 13.7	42.2 ± 18.4	<0.71
E/A tricuspid	1.1 ± 0.33	1.3 ± 1.1	1.2 ± 0.8	<0.51
E′ tricuspid, cm/s	10.2 ± 2.5[a]	7.1 ± 2.9	8.1 ± 3.2	<0.0001
E/E′ tricuspid	4.9 ± 1.6[a]	8.1 ± 4.8	7.8 ± 4.3	<0.009
S′ tricuspid, cm/s	13.1 ± 3.3[a]	10.1 ± 2.7	8.7 ± 3.3	<0.0001
TAPSE, mm	22.9 ± 3.4[a]	16.8 ± 4.1	15.8 ± 3.7	<0.0001
PET, ms	279 ± 27.3	263.9 ± 39	276.2 ± 39.1	<0.15
RV MPI	0.32 ± 0.16	0.45 ± 0.26	0.51 ± 0.31[c]	<0.01
PASP, mm Hg	27.5 ± 8.1[a]	39.5 ± 11.9	40.6 ± 11.8	<0.0001
RV longitudinal strain %	−16.8 ± 7.7[a]	−10 ± 4.2	−8.1 ± 3.7	<0.0001

Abbreviations: A, late diastolic trans tricuspidal diastolic flow; C-AL, cardiac AL amyloidosis; E, early peak transtricuspid diastolic flow; E′, lateral tricuspid annulus-derived early diastolic flow; MPI, myocardial performance index; NC-AL, noncardiac AL amyloidosis; PASP, pulmonary artery systolic pressure; PET, pulmonary valve ejection time; RV, right ventricular; RVEDD, RV end-diastolic diameter; RVFW, RV free wall thickness; S′, lateral tricuspid annulus peak systolic velocity; TAPSE, tricuspid annulus systolic plane excursion; TTR, transthyretin-related amyloidosis.
Scheffe's post hoc analysis:
[a]NC-AL vs others, $P < 0.05$. [b]TTR vs others, $P < 0.05$. [c]NC-AL vs C-AL, $P < 0.05$.

could be a less aggressive disease with a slower progressive course, probably due to the lower deposition rate of the amyloid protein and to the absence of the intrinsic cardiotoxic effect of circulating light chains. In ATTR, a slower deposition of amyloid fibers could let the heart predispose compensatory mechanisms that might slow down the onset of HF symptoms, justifying the lower NT-proBNP plasma levels. In addition, a lesser extent of a direct toxic effect might be postulated to explain these results.

Limitations

The study presents all the limitations of a cross-sectional design. As no survival data analysis was performed, longitudinal observational studies are needed to determine the prognostic value of the echocardiographic differences detected at baseline.

Our choice to group together ATTRm and ATTRwt patients might be criticized. However, in our population, the ATTRm and the ATTRwt phenotypes were similar in terms of cardiac involvement, echocardiographic profile, and age at diagnosis. A second limitation is the lack of biopsy evidence of amyloid in 32% of ATTRwt amyloidosis patients. However, this cohort of patients was fully characterized with all other clinical investigative techniques currently available. When combined, these are known to provide high diagnostic accuracy.[30,31]

Conclusion

On the basis of the aforementioned considerations, we may hypothesize that we are observing different diseases at a different temporal point of view. AL amyloidosis has a quick progression rate, becomes rapidly symptomatic, and the involvement of other organs can help the diagnostic process. On the other hand, TTR amyloidosis could have a slow progression rate, remaining poorly symptomatic for a greater amount of time. In addition, especially in our population, in which ATTRm has mostly a cardiac phenotype with late onset,[32] therefore being comparable with ATTRwt, the absence of neurological manifestations or other major organ system involvement may be a further cause of under-recognition. The validity of our considerations should be corroborated by longitudinal observations starting from ATTRm carriers.

References

1. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. *N Engl J Med.* 2003;349:583–596.
2. Perfetto F, Cappelli F, Bergesio F, et al. Cardiac amyloidosis: the heart of the matter. *Intern Emerg Med.* 2013;8:191–203.
3. Smorti M, Cappelli F, Guarnieri S, et al. Depression and cardiac symptoms among AL amyloidosis patients: the mediating role of coping strategies. *Psychol Health Med.* 2014;19:263–272.
4. Smorti M, Cappelli F, Bergesio F, et al. Anxiety and depression among AL amyloidosis patients: the role of cardiac symptoms. *Amyloid.* 2012;19:123–128.
5. Rapezzi C, Merlini G, Quarta CC, et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. *Circulation.* 2009;120:1203–1212.
6. Koyama J, Ray-Sequin PA, Falk RH. Longitudinal myocardial function assessed by tissue velocity, strain, and strain rate tissue Doppler echocardiography in patients with AL (primary) cardiac amyloidosis. *Circulation.* 2003;107:2446–2452.
7. Porciani MC, Lilli A, Perfetto F, et al. Tissue Doppler and strain imaging: a new tool for early detection of cardiac amyloidosis. *Amyloid.* 2009;16:63–70.
8. Porciani MC, Cappelli F, Perfetto F, et al. Rotational mechanics of the left ventricle in AL amyloidosis. *Echocardiography.* 2010;27:1061–1068.
9. Bellavia D, Pellikka PA, Dispenzieri A, et al. Comparison of right ventricular longitudinal strain imaging, tricuspid annular plane systolic excursion, and cardiac biomarkers for early diagnosis of cardiac involvement and risk stratification in primary systematic (AL) amyloidosis: a 5-year cohort study. *Eur Heart J Cardiovasc Imaging.* 2012;13:680–689.
10. Cappelli F, Porciani MC, Bergesio F, et al. Right ventricular function in AL amyloidosis: characteristics and prognostic implication. *Eur Heart J Cardiovasc Imaging.* 2012;13:416–422.
11. Liu D, Niemann M, Hu K, et al. Echocardiographic evaluation of systolic and diastolic function in patients with cardiac amyloidosis. *Am J Cardiol.* 2011;108:591–598.
12. Rapezzi C, Quarta CC, Riva L, et al. Transthyretin-related amyloidoses and the heart: a clinical overview. *Nat Rev Cardiol.* 2010;7:398–408.
13. Sattianayagam PT, Hahn AF, Whelan CJ, et al. Cardiac phenotype and clinical outcome of familial amyloid polyneuropathy associated with transthyretin alanine 60 variant. *Eur Heart J* 2012;33:1120–1127.
14. Ranlov I, Alves IL, Ranlov PJ, et al. A Danish kindred with familial amyloid cardiomyopathy revisited: identification of a mutant transthyretin-methionine111 variant in serum from patients and carriers. *Am J Med.* 1992;93:3–8.

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22353

15. Buxbaum J, Alexander A, Koziol J, et al. Significance of the *Amyloidogenic Transthyretin* Val 122 Ile allele in African-Americans in the Arteriosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) Studies. *Am Heart J.* 2010;159:864–870.
16. Rapezzi C, Quarta CC, Obici L, et al. Disease profile and differential diagnosis of hereditary transthyretin-related amyloidosis with exclusively cardiac phenotype: an Italian perspective. *Eur Heart J.* 2013;34:520–528.
17. Dubrey S, Cha K, Skinner M, et al. Familial and primary (AL) cardiac amyloidosis: echocardiographically similar diseases with distinctly different clinical outcomes. *Heart.* 1997;78:74–82.
18. Ng B, Connors LH, Davidoff R, et al. Senile systemic amyloidosis presenting with heart failure: a comparison with light chain-associated amyloidosis. *Arch Intern Med.* 2005;165:1425–1429.
19. Ogiwara F, Koyama J, Ikeda S, et al. Comparison of the strain Doppler echocardiographic features of familial amyloid polyneuropathy (FAP) and light-chain amyloidosis. *Am J Cardiol.* 2005;95:538–540.
20. Perugini E, Guidalotti PL, Salvi F, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. *J Am Coll Cardiol.* 2005;46:1076–1084.
21. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461–470.
22. 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. *Am J Hematol.* 2005;79:319–328
23. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005;18:1440–1463.
24. Tei C, Ling LH, Hodge DO, et al. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function: a study in normals and dilated cardiomyopathy. *J Cardiol.* 1995;26:357–366.
25. Ganau A, Devereux RB, Roman MJ, et al. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. *J Am Coll Cardiol.* 1992;19:1550–1558.
26. Quarta CC, Solomon SD, Uraizee I, et al. Left ventricular structure and function in transthyretin-related versus light-chain cardiac amyloidosis. *Circulation.* 2014;129:1840–1849.
27. Brenner DA, Jain M, Pimentel DR, et al. Human amyloidogenic light chains directly impair cardiomyocyte function through an increase in cellular oxidant stress. *Circ Res.* 2004;94:1008–1010.
28. Perlini S, Palladini G, Vezzoli M. Reduction of circulating amyloidogenic light chains improves myocardial function and survival despite unaltered amount of amyloid myocardial deposits. *Circulation*. 2004;110(suppl 3):602.
29. Migrino RQ, Truran S, Gutterman DD, et al. Human microvascular dysfunction and apoptotic injury induced by AL amyloidosis light chain proteins. *Am J Physiol Heart Circ Physiol.* 2011;301:H2305–H2312.
30. Fontana M, Banypersad SM, Treibel TA, et al. Native T1 mapping in transthyretin amyloidosis. *JACC Cardiovasc Imaging.* 2014;7:157–165.
31. Hutt DF, Quigley AM, Page J, et al. Utility and limitations of 3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy in systemic amyloidosis. *Eur Heart J Cardiovasc Imaging.* 2014;15:1289–1298.
32. Perfetto F, Cappelli F, Bergesio F. Asymptomatic homozygous gene carrier in a family with Ile68Leu ATTR amyloidosis: a new endemic region in northern Tuscany? *J Cardiovasc Med (Hagerstown)*. 2011;12:450–451.

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22353