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Right ventricular function in AL amyloidosis: characteristics and prognostic implication

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Aim The importance of right ventricle (RV) dysfunction in AL amyloidosis has been underestimated. This study was designed to comprehensively evaluate RV function and its prognostic role in patients with AL amyloidosis with and without echocardiographic evidence of cardiac involvement.

Method and results Fifty-two biopsy-proven AL amyloidosis patients underwent a thorough echocardiographic evaluation. Twenty-seven patients (CA) met the international echocardiographic criteria for cardiac involvement [left ventricular (LV) wall thickness $\geq$12 mm] and 25 patients had no cardiac amyloidosis features (NCA). Patients were compared with a sex- age-matched control group. Patients and controls underwent traditional, tissue Doppler (TDI), speckle-tracking left and RV echocardiographic evaluation. No difference was observed between groups in RV diastolic diameter, whereas CA patients showed increased RV free wall thickness ($P < 0.0001$). Compared with controls and NCA patients, traditional echocardiography, TDI, and speckle-tracking evaluation detected significantly ($P < 0.0001$) depressed RV longitudinal systolic function in CA patients. No difference was observed between groups at Doppler diastolic evaluation, whereas at tricuspidal annulus TDI analysis, CA subject showed significantly lower E′ and A′ values with increased *E*/*E*′ ratio ($P < 0.0001$). Over a 19 months median follow-up period, 18 patients died. Cox multivariate analysis showed that N-terminal pro-Brain natriuretic peptide and RV longitudinal strain were the strongest death predictor.

Conclusion Our data show that in patients with AL amyloidosis, RV involvement develops later than LV amyloid deposition but when it occurs, prognosis dramatically worsens. Moreover RV longitudinal strain was the only echocardiographic predictor of prognosis. We suggest that RV function analysis should be performed routinely as a part of echocardiographic evaluation in these patients.

Keywords AL amyloidosis • Right ventricular • Speckle-tracking echocardiography • Longitudinal strain

Introduction

Amyloidosis is a rare systemic disease characterized by extracellular deposition of protein-derived fibrils in various tissues and organs, including the heart; they are characterized by a β-sheet structure with typical apple-green birefringence when viewed under polarized light after Congo Red staining.[1] Although almost every amyloidogenic protein may be complicated with cardiac amyloidosis (CA), the actual prevalence of heart involvement is widely variable among the different types of amyloidosis, being uncommon in amyloidosis associated with chronic inflammatory diseases (AA), and very frequent in immunoglobulin light chains (AL) and hereditary (mainly TTR mutation) related forms.

Cardiac involvement is one of the main prognosis determinants of systemic amyloidosis, and among the three different forms of CA, AL has the worst prognosis.[2] Since the hallmark of CA is represented by a restrictive cardiomyopathy, attention has been traditionally focused on left ventricular (LV) diastolic function.[3,4]

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In the last few years, by means of more advanced echocardiographic techniques, such as tissue Doppler imaging (TDI) and two-dimensional (2D) speckle-tracking echocardiography, attention has been turned to various alterations of LV systolic function.[5–8]

On the other hand the importance of right ventricle (RV) involvement has often been underestimated in CA patients, and the role of its contractile and systo-diastolic performance was undervalued. Nowadays, few data are available about RV involvement in amyloidosis, mainly focusing on chamber enlargement and RV systolic function.[9–11] Moreover, little is known about the relationship between RV dysfunction and LV dysfunction.

Recently, 2D speckle-tracking echocardiography has enabled to analyse myocardial strain avoiding Doppler limitation, in particular, angle dependency. This was especially useful in RV myocardial strain analysis due to its particular geometry.

The aim of the present study is to comprehensively evaluate right ventricular function by means of traditional, TDI, and 2D speckle-tracking echocardiography in AL amyloidosis patients, both with and without echocardiographic evidence of cardiac involvement. Moreover, we investigate whether RV involvement is associated with poor prognosis, when compared with already assessed prognostic markers, such as N-terminal pro-Brain natriuretic peptide (NT-proBNP).[12]

Methods

Fifty-two consecutive patients (34 females and 18 males, mean age 69.3 $\pm$ 10.3 years) with biopsy-proven AL amyloidosis were examined at the Tuscan Regional Centre of Amyloidosis, Florence, Italy between February 2007 and December 2010. The positive biopsy site was abdominal fat in 35 patients (66%), kidney in 6 (12%), myocardium in 5 (10%), salivary gland in 3 (6%), rectum in 2 (4%), and liver in 1 (2%). All positive biopsies demonstrated typical Congo Red birefringence under polarized light. AL amyloidosis was confirmed by the finding of a monoclonal protein in the serum or urine and/or a monoclonal population of plasma cells in the bone marrow, when evaluated by immunohistochemistry. Hereditary amyloidosis was excluded by DNA analysis in all patients. At the time of diagnosis, patients were referred to our echo laboratory in the setting of a multidisciplinary evaluation. Exclusion criteria were the presence of hypertension, coronary artery disease, valvular disease, or diabetes to avoid confounding interaction in echocardiographic variables.

Patients were classified as having CA if the mean value of LV wall thickness [half of the sum of ventricular septum and posterior wall (PW) thickness] was $\geq$12 mm or not echocardiographic evident CA (NCA) if this criterion was not satisfied. A total of 31 asymptomatic sex- and age-matched subjects (mean age 67.4 $\pm$ 8.5 years) recruited among healthy volunteers was analysed as the control group. None of them had a history of previous or current heart disease, systemic hypertension, or diabetes or was on medications. All had a normal physical examination, as well as electrocardiographic and echocardiographic findings. All participants gave informed written consent, and the study was approved by the local Ethics Committee. In all patients and healthy subjects a complete M-mode, 2D, conventional Doppler, tissue Doppler, and speckle-tracking imaging evaluation was performed. Echocardiographic evaluation was performed by a single experienced echocardiographer (F.C.), who was blinded to the clinical history of the patient. NT-proBNP levels were measured with an electrochemiluminescence sandwich immunoassay (ECLIA, Roche). Creatinine clearance, using MDRD formula[13] and both systolic and diastolic arterial blood pressure were evaluated. Follow-up visits were scheduled every 3 months and time to death was calculated from the date of the echocardiographic evaluation.

Standard and tissue Doppler imaging echocardiography

Images were obtained using a cardiac ultrasound machine (Vivid 7 System, Vingmed, General Electric, Horten, Norway) equipped with a 3S probe. The following echo M-mode, bidimensional, and pulsed Doppler parameters were evaluated; end-diastolic thickness of the interventricular septum (IVS) and of the LV PW; LV end-diastolic and end-systolic diameter (LVEDD, LVESD, respectively); body surface area (BSA)-indexed LV mass ($LVmass_{ind}$); relative wall thickness (RWT), LV endocardial fractional shortening (FS); left atrial area evaluated from the apical four-chamber view at the end of systole; LV end-diastolic and end-systolic volumes (LVEDV and LVESV, respectively). Ejection fraction (EF) estimated with the biplane Simpson method; mitral and tricuspidal peak flow velocity in early and in late diastole, during atrial contraction (E and A, respectively), *E/A* ratio; LV and RV myocardial performance index (MPI), i.e. the sum of isovolumetric contraction and relaxation times divided by the ejection time, as previously described[14]; RV free wall thickness (RVFW); RV end-diastolic diameter (RVEDD) evaluated from parasternal long-axis view; and the systolic displacement of the lateral portion of the tricuspid annular plane (TAPSE). Pulmonary artery systolic pressure (PASP) assess was obtained by adding to the transtricuspid pressure gradient an estimate of the right atrial pressure. Pulsed TDI-derived early diastolic peak velocity at the mitral annulus (E′), as an index of LV relaxation and the *E/E′* ratio, as an index of the LV filling pressure, were also evaluated.[15] Lateral tricuspid annulus pulsed TDI-derived early and late diastolic peak velocities (E′, A′, and the ratio E′/A′), peak systolic velocity (S′), and the *E/E′* ratio, as an index of the RV filling pressure, were also evaluated.

All these parameters were evaluated to achieve a more complete assessment of both the systolic and diastolic function in the RV and the LV.

Speckle-tracking echocardiography

After completion of the standard echocardiographic examination, 2D greyscale apical four-chamber, two-chamber, long-axis views, at high frame rates (80–100 frame/s) were stored to assess speckle-tracking-derived LV and RV longitudinal strain. Using commercially available 2D strain software (Echopac PC, version 6.0.1, GE Healthcare, Milwaukee, WI, USA), the endocardial border of the end-systolic frame was manually traced. From these recordings, Echopac selected the speckles and tracked them during the cardiac cycle.

LV longitudinal strain (LV LongSt) expressed as the average of the three apical views, and RV (RV LongSt) longitudinal strain expressed as the average of the three free wall segments in the apical four-chamber view were evaluated.

Statistical analysis

Data are expressed as the mean $\pm$ SD. Differences between Control, NCA, and CA groups were analysed with one-way ANOVA, and *post hoc* analyses were performed using Scheffe's method. Area under the receiver-operating characteristics curve (ROC) analysis was performed to determine the prognostic value and to determine the optimal cut-off. Sensitivity, specificity, positive predicted value (PPV), and negative predicted value using relevant cut-offs were computed. Survival analysis was performed according to the Cox regression method.

The endpoint of survival analysis was cardiac death. Survival curves were plotted with the method of Kaplan and Meier using the log-rank test for comparisons.

A stepwise regression analysis was performed to investigate the independence of the mean RV strain from several echocardiographic variables (IVS, RVFW, *E/E′* ratio, and PASP). A 0.05 level of significance was applied to determine whether variables were added or removed from the model.

All statistical analyses were performed using SPSS 13.0 statistical software for Windows (SPSS, Inc., Chicago, IL, USA). Values of $P < 0.05$ were considered statistically significant.

Results

The study population consisted of 31 healthy sex- and age-matched subjects (control group) and 52 patients with systemic AL amyloidosis. According to half of the sum of ventricular septum and PW thickness $\geq$12 mm criterion, 27 AL patients had CA, whereas the other 25 did not have echocardiographic evidence of cardiac involvement (NCA group). All control subjects and NCA patients were asymptomatic, whereas among the CA group, 4 patients were in NYHA class IV, 8 in NYHA class III, and 13 in NYHA II. Serum NT Pro-BNP concentration was 1640 $\pm$ 4746 pg/mL in NCA and 9954 $\pm$ 12 519 pg/mL in CA patients ($P < 0.001$). No difference was observed between NCA and CA patients in the glomerular filtration rate and in both the systolic (125.7 $\pm$ 18.4 vs. 116.5 $\pm$ 18.6 mmHg) and diastolic (75.2 $\pm$ 12.2 vs. 68.8 $\pm$ 10.7 mmHg) arterial pressure.

Left ventricular dimension and systo-diastolic function

As reported in *Table 1*, NCA patients did not differ from control subjects in terms of LV wall thickness, indexed LV mass, and RWT. By definition, LV wall thickness, indexed LV mass, and RWT were significantly higher in CA patients than in the other two groups. LVEDD and LVESD were significantly smaller in CA patients than in control subjects, whereas no differences were found with regard to LVEDV and LVESV. In NCA patients, the atrial area was significantly larger than in control subjects, and significantly smaller when compared with the CA group. As to the diastolic function, CA patients showed a higher *E/A* ratio than the other groups, whereas in the NCA group, *E′* value was significantly lower than in control subjects and higher than in CA patients. A progressive increase in the *E/E′* ratio was observed in the three groups, mean values being significantly lower in control subjects and higher in CA patients, when compared with the NCA group. LV MPI was significantly higher in CA than in both the NCA and control groups. The EF was superimposable in the three groups, whereas LV FS was significantly reduced only in CA patients. Moreover, LV LongSt was similar in control subjects and NCA patients, whereas it was significantly reduced in CA patients.

Right ventricular dimension and systo-diastolic function

As reported in *Table 2*, no difference was found in RV diastolic diameter among groups. RVFW thickness was superimposable in control subjects and NCA patients, whereas it was significantly increased in CA patients. No difference was observed between groups at traditional Doppler diastolic evaluation, while at tricuspidal annulus TDI analysis, CA subjects showed significantly lower E′ and A′ values with increased *E/E′* ratios. RV systolic function was similar in control subjects and NCA patients. In contrast, RV longitudinal function was significantly depressed in CA patients, when analysed by traditional echocardiography, TDI, and 2D speckle-tracking evaluation. Moreover, a significant increase in PASP values was observed only in CA patients.

Prognostic relevance of right ventricle function and left ventricular function

Over a mean follow-up period of 19 $\pm$ 12 months (median 20 months), 18 patients died (35%), all but one deaths being either sudden or due to CHF. One patient died from complications due to multiple myeloma. As expected, patients with evidence of ecocardiographic cardiac involvement showed significantly poorer prognosis than NCA patients (*Figure 1*). *Table 3* reports the Cox proportional hazard analysis of various clinical and echocardiographic predictors of long-term mortality in all patients with AL amyloidosis (52 patients). On univariate analysis, several variables were found to be significantly ($P < 0.05$) related to survival, i.e. NT-proBNP levels, LV IVS thickness, RVFW thickness, TAPSE, tricuspidal E′ and *E/E′*, mean RV and LV Long Strain By multivariate regression analysis, NT-proBNP levels ($P = 0.006$) and RV Long Strain remained the strongest predictors ($P = 0.048$) of the primary outcome. RV longitudinal strain had the most reliable diagnostic power for survival compared with other echocardiographic parameters of RV dysfunction by ROC curves, with an area under the curve equal to 0.790. With a $-$17% cut-off value (*Figure 2A*), sensitivity was 65.5%, specificity 90%, PPV 64%, and PPN 85%. This cut-off discriminated the two groups with a highly significant survival difference: 9 months vs. not reached (*Figure 2B*; $P < 0.0001$). Among the different echocardiographic parameters, RV LongSt was significantly correlated with IVS thickness ($R = 0.585$; $P < 0.0001$), RVFW ($R = 0.299$; $P < 0.03$), and *E/E′* ratio values ($R = 0.445$; $P < 0.001$), but not with PASP ($R = 0.256$; $P > 0.05$). According to stepwise regression analysis, only IVS was independently correlated to RV longitudinal strain ($R = 0.585$; $P < 0.0001$).

Discussion

The main result of our study is that in cardiac AL amyloidosis RV longitudinal systolic dysfunction, as assessed by depressed RV longitudinal strain, is a negative prognostic marker. As a collateral finding, we found that in patients with AL amyloidosis, impairment of LV ventricular diastolic function is the first functional sign of cardiac involvement, since E′ reduction, *E/E′* ratio increase, and left atrial enlargement were observed even before the amyloid infiltration process had produced LV wall thickening. At such an early stage of the disease, no sign of RV or LV systolic impairment was observed by either traditional or TDI echocardiography, and patients were asymptomatic. It should be noted that these patients did not meet the accepted echocardiographic criterion of cardiac involvement, based on the mean value of wall thickness.[16]

Table 1 Left ventricular echocardiographic characteristics between controls and patients with AL amyloidosis without and with cardiac involvement

	Controls ($n = 31$)	NCA ($n = 25$)	CA ($n = 27$)	*P*-value
LV IVS, mm	9.8 ± 1	10.3 ± 0.9	15.6 ± 2.8*	<0.0001
LV PW, mm	9.8 ± 0.8	10.2 ± 1.2	15.7 ± 2.2*	<0.0001
LV mass index, g/m^2	89 ± 19	94 ± 18	160 ± 29*	<0.0001
RWT, mm	0.42 ± 0.04	0.46 ± 0.05	0.76 ± 0.22*	<0.0001
LVEDD, mm	46 ± 5	44 ± 4	42 ± 6**	<0.05
LVESD, mm	28 ± 5	27 ± 5	25 ± 3**	<0.05
FS%	39 ± 6.5	42.9 ± 5.7	34.5 ± 8.8*	<0.0001
LA area cm^2	16.2 ± 2.8***	18.5 ± 3****	23.05 ± 3.6*	<0.0001
LVEDV, mL	90 ± 26	78 ± 20	75 ± 22	NS
LVESV, mL	34 ± 11	32 ± 13	30 ± 12	NS
EF%	62 ± 5	59 ± 9	59 ± 7	NS
E, cm/s	62 ± 11***	75 ± 17	78 ± 21	<0.0001
A, cm/s	66 ± 17	91 ± 21****	55 ± 23	<0.0001
E/A	0.99 ± 0.24	0.85 ± 0.18	1.73 ± 0.98*	<0.0001
E′, cm/s	9.4 ± 2.3***	7.4 ± 1.6****	4.4 ± 1.1*	<0.0001
E/E′	7 ± 2.2***	10.6 ± 3.4****	18.9 ± 7.9*	<0.0001
LV MPI	0.4 ± 0.12	0.36 ± 0.12	0.55 ± 0.21*	<0.0001
LV Long Strain%	−19.2 ± 6.6	−17.7 ± 4.4	−9.8 ± 4*	<0.0001

LV, left ventricular; IVS, interventricular septum thickness; PW, posterior wall thickness; RWT, relative wall thickness LVEDD, LV end-diastolic diameter; LVESD, LV end-systolic diameter; FS, fractional shortening; LA, left atrium; LVEDV, LV end-diastolic volume LVESV, LV end-systolic volume; EF, ejection fraction; E, early diastolic mitral peak flow velocity; A, late diastolic mitral peak flow velocity; MPI, myocardial performance index; Long Strain, longitudinal strain; E′, early diastolic peak velocity at lateral mitral annulus. Scheffe's *post hoc* analysis:
*$P < 0.0001$ CA vs. others;
**$P < 0.05$ Cardiac Amyloidosis vs. controls;
***$P < 0.0001$ CA vs. others;
****$P < 0.0001$ NCA vs. others.

Table 2 Right ventricular echocardiographic characteristics between controls and patients with AL amyloidosis without and with cardiac involvement

	Controls ($n = 31$)	NCA ($n = 25$)	CA ($n = 27$)	*P*-value
RVEDD, mm	25.8 ± 4	24.7 ± 5.2	26.9 ± 4.3	NS
RVFW thickness, mm	5.1 ± 1	5.6 ± 1.2	7.1 ± 0.9*	<0.0001
E, cm/s	42 ± 8	46 ± 10.3	48 ± 15	NS
A, cm/s	37 ± 9	42.1 ± 10.7	41.6 ± 12	NS
E/A	1.18 ± 0.27	1.14 ± 0.28	1.22 ± 0.49	NS
E′, cm/s	11.7 ± 2.9	9.9 ± 2.8	6.6 ± 3*	<0.0001
A′, cm/s	14.7 ± 3.7	15.7 ± 3.9	10.7 ± 3.9*	<0.0001
S′, cm/s	13.2 ± 2.3	12.7 ± 3.5	10 ± 2.9*	<0.0001
E/E′	3.9 ± 1.3	4.6 ± 2	8.6 ± 5.4*	<0.0001
E′/A′	0.83 ± 0.28$	0.6 ± 0.22	0.65 ± 0.33**	<0.01
RV Long Strain%	−24.9 ± 5.8	−23.5 ± 5.3	−16.7 ± 7.1*	<0.0001
MPI, dx	0.33 ± 0.28	0.35 ± 0.18	0.42 ± 0.26	NS
TAPSE, mm	23.7 ± 3.7	22.8 ± 3.2	16.5 ± 4.4*	<0.0001
PASP, mmHg	25.2 ± 4.5	27.5 ± 11.4	37.4 ± 8.2*	<0.0001

RV, right ventricular; RVEDD, RV end-diastolic diameter; RVFW, RV free wall thickness; E, early peak transtricuspidal diastolic flow; A, late diastolic trans tricuspidal diastolic flow; E′, Lateral tricuspid annulus-derived early diastolic flow; A′ lateral tricuspid annulus-derived late diastolic flow; S′, peak systolic velocity; Long Strain, longitudinal strain; MPI, myocardial performance index; TAPSE, tricuspid annulus systolic plane excursion; PASP, pulmonary artery systolic pressure. Scheffe's *post hoc* analysis:
*$P < 0.001$ CA vs. controls and NCA;
**$P < 0.01$ CA vs. controls.

Interestingly, mean NT-proBNP levels of this group of patients were significantly increased (1640 ± 4746 pg/mL), probably due to the diastolic dysfunction secondary to early amyloid infiltration, before the onset of LV wall thickening. Along with the progression of cardiac involvement associated with a progressive increase in wall thickening, further deterioration of diastolic function and impairment of systolic function as expressed by longitudinal strain become evident, for both the LV and the RV. At this more advanced stage, patients become symptomatic, mirroring the clinical features of heart failure with preserved EF in which, combined with the typical LV structural changes, alterations of both diastolic function and long-axis systolic function of the RV have already been described.[17,18] Interestingly, our results indicate that diastolic dysfunction of the right ventricle occurs later than that of the LV. Indeed, in NCA patients, only subtle alterations of RV diastolic function were observed when LV diastolic dysfunction had become evident. Usually, right ventricular dysfunction is often present in LV pathologies as a consequence of direct disease extension, afterload changes, or ventricular interdependence.[19] Although RV wall thickening and elevated pulmonary pressure observed in our CA patients could be a sign of both disease extension and RV afterload changes, it appears that ventricular interdependence plays an important role in inducing a progressive deterioration of right ventricular function. In a series of 74 AL amyloid patients Ghio *et al.*[10] showed that, despite similar RV wall thickness, patients with low TAPSE had thicker LV walls and a more compromised LV function, indicating that the LV involvement itself rather than RV amyloid infiltration is an important determinant of RV dysfunction. The present study supports and further extends this concept, since stepwise analysis demonstrated that interventricular septum thickness was the only independent predictor of RV longitudinal strain.

It is now well known that normal RV performance is strictly dependent on LV function. Because of its anatomical position, the interventricular septum has been identified as a key element for ventricular interaction.[20] Altered RV relaxation was observed in patients with septal hypertrophic cardiomyopathy by Severino *et al.*,[21] also showing a direct relation between this alteration and septal wall thickness: the higher the septal hypertrophy, the

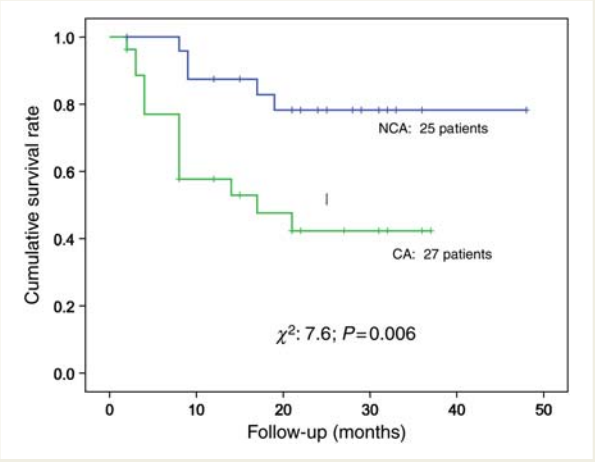

Figure 1 Univariate Kaplan–Meier survival analysis of the study population separated based on cardiac involvement (log-rank statistics: χ^2: 7.6; $P = 0.006$).

Table 3 Cox proportional hazard analysis of various clinical and echocardiographic predictors of long-term mortality in all patients with cardiac amyloidosis (52 patients)

Variable	Univariate		Multivariate	
	Hazard ratio (confidence interval 95%)	*P*-value	Hazard ratio (confidence interval 95%)	P-value
NTproBNP	1.000 (1.000–1.000)	<0.0000	1.000 (1.000–1.000)	0.006
LV IVS	1.255 (1.115–1.412)	<0.000	0.697 (0.476–1.021)	0.06
EF	0.972 (0.930–1.016)	0.2		
RVFW thickness	1.430 (1.021–2.004)	0.038	0.966 (0.519–1.799)	0.9
RVEDD	1.095 (0.980–1.223)	0.1		
LV E/A	1.287 (0.794–2.087)	0.3		
LV E′	0.782 (0.596–1.096)	0.076		
LV *E/E′*	1.042 (0.986–1.101)	0.14		
PASP	1.039 (0.994–1.086)	0.09		
TAPSE	0.840 (0.758–0.931)	0.001	0.892 (0.651–1.222)	0.4
RV E′	1.032 (1.001–1.064)	0.04	1.035 (0.920–1.165)	0.5
RV *E/E′*	1.150 (1.057–1.250)	0.001	2.903 (0.382–22.089)	0.3
Mean RV Long Strain	1.128 (1.025–1.241)	0.01	1.192 (1.001–1.421)	0.048
Mean LV Long Strain	1.183 (1.055–1.328)	0.004	1.085 (0.891–1.322)	0.4

NTproBNP, N-terminal pro Brain Natriuretic Peptide; LV, left ventricular; IVS, interventricular septum thickness; EF, ejection fraction; RV, right ventricular; RVFW, RV free wall thickness; RVEDD, RV end-diastolic diameter; E/A, ratio of early diastolic mitral peak flow velocity and late diastolic mitral peak flow velocity; E′, early diastolic peak velocity at lateral mitral annulus; PASP, pulmonary artery systolic pressure; TAPSE, systolic displacement of the lateral portion of the tricuspid annular plane; RV E′, RV lateral tricuspid annulus-derived early diastolic peak velocity; RV *E/E′*, ratio of early diastolic tricuspidal peak flow velocity and lateral tricuspid annulus-derived early diastolic peak velocity; RV longitudinal strain; LV, Long Strain; LV, longitudinal strain.

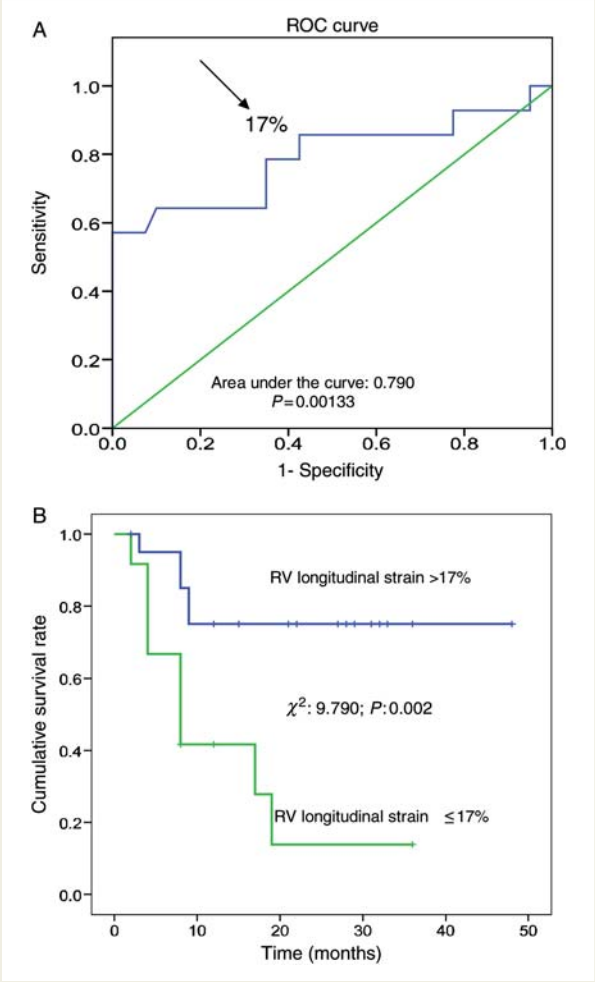

Figure 2 (*A*) The receiver-operator characteristic analysis for the study population indicated that a RV longitudinal strain value of—17% was the most suitable cut-off value to predict all death. (*B*) In the study population, the receiver-operator characteristic curve-derived cut-off value of RV longitudinal strain of −17. % predicted mortality (χ^2: 9.790; $P < 0.002$).

more depressed is the RV relaxation index. To date, many reports have clearly demonstrated the prognostic importance of the right ventricular systolic function in patients with heart failure of both ischaemic and non-ischaemic aetiology.[22–25] Moreover, several echocardiographic parameters of right ventricular function have been found to possess independent prognostic power. Karatasakis *et al.*[26] proposed RV shortening as an easily obtainable measure of RV systolic performance to be used as a prognostic indicator in patients with end-stage heart failure. Meluzin *et al.*[27] described systolic and diastolic tricuspid annular velocity derived from pulsed-wave Doppler tissue imaging as an independent predictor of cardiac events. In cardiac AL heart failure patients, Ghio *et al.* showed that TAPSE values <17 mm identify a subgroup with poor prognosis, with a significant univariate association with survival of both TAPSE and NT-proBNP plasma levels.[10]

Accordingly, the present study showed that, in patients with AL amyloidosis, an RV longitudinal strain less negative than −17% identifies a cohort of patients with marked RV dysfunction and a high risk of death. The prognostic significance of RV longitudinal strain persisted after adjusting for the cardiac biomarker NT-proBNP, for indexes of systolic and diastolic LV function, for PASP and for diastolic RV dysfunction, as assessed by tricuspidal E′ and *E*/*E*′. This piece of information adds on the already well-known prognostic role of NT-proBNP serum levels, and it should be noted that RV longitudinal strain was the only echocardiographic predictor of prognosis, resulting superior to the standard 2D, Doppler flow measurements, and simple tissue velocity indexes.

Therefore, RV longitudinal strain should be added to TAPSE[10] as a valuable RV-derived prognostic marker in patients with cardiac AL amyloidosis. The higher sensitivity of longitudinal strain observed in the present study could be explained by the fact that it reflects the whole RV free wall rather than only tricuspidal annular deformation.

Surprisingly, prior echocardiographic findings that had been associated with mortality, such as ventricular thickness,[28] mitral inflow deceleration time, and the *E*/*A*[29] and *E*/*E*′ ratios did not qualify in the final model. This may be due to the strong association of these variables with the heart failure class or the other independent markers such as NT-proBNP.[30] This observation is consistent with a recent study by Rapezzi *et al.*,[2] who recruited a greater study population with a median follow-up period of ∼9 years. However, although the echocardiographic parameters of diastolic dysfunction are not independent predictors of survival for these patients, identifying diastolic dysfunction is useful for early detection and risk stratification in patients with AL amyloidosis.

Our results show that amyloid infiltration of the LV particularly at the septum plays a major role in determining both systolic and diastolic dysfunction of the RV. Once the latter develops, the prognosis of AL patients dramatically worsens. However, due to the small number of patients and the low number of events, this observation must be considered preliminary and needs to be confirmed in larger trials.

Conclusion

CA is challenging to diagnose and monitor. Over the past decade, development of new imaging techniques such as magnetic resonance, TDI, and speckle-tracking imaging has enabled us not only to better understand the disease, but also to explore the different stages through which the disease progresses. The results of this study suggest that assessment of RV function can provide valuable information about the stage and prognosis of amyloidosis.

Thus we suggest that analysis of RV function should be performed routinely as a part of cardiac amyloidosis assessment.

Conflict of interest: none declared.

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