Native T1 and ECV in ATTR amyloidosis

Ana Martinez-Naharro MD[a*], Tushar Kotecha MBChB[ab*], Karl Norrington MBBS[a**], Michele Boldrini MD[a], Tamer Rezk MBBS[a], Candida Quarta MD, PhD[a], Thomas A Treibel PhD[bc], Carol J Whelan MD[a], Daniel S Knight MD[a], Peter Kellman PhD[d], Frederick L. Ruberg MD[e], PhD[e], Julian D. Gillmore MD, PhD[a], James C. Moon MD[bc], Philip N Hawkins PhD [a], Marianna Fontana MD, PhD[a]

[a] National Amyloidosis Centre, Division of Medicine, University College London, Royal Free Hospital, London, UK
[b] Institute of Cardiovascular Science, University College London, London, UK
[c] Barts Heart Centre, West Smithfield, London, UK
[d] National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA.
[e] Amyloidosis Center and Section of Cardiovascular Medicine, Department of Medicine, Boston University School of Medicine, Boston Medical Center

*Ana Martinez-Naharro and Tushar Kotecha contributed equally to this work
** Karl Norrington is deceased

Word count: 4499
Running title: Tissue characterisation by CMR in ATTR amyloidosis

Address for Correspondence
Dr Marianna Fontana MD, PhD
National Amyloidosis Centre, University College London, Royal Free Hospital
Rowland Hill Street
London. NW3 2PF, UK.
E-mail: m.fontana@ucl.ac.uk
Phone No: +44 20 7433 2764
Fax No: +44 20 7433 2803

ABSTRACT
Objectives: To evaluate the prognostic potential of native myocardial T1 in cardiac transthyretin amyloidosis (ATTR) and compare native T1 with extracellular volume (ECV) in terms of diagnostic accuracy and prognosis.
Background: ATTR amyloidosis is an increasingly recognised cause of heart failure that has an overlapping clinical phenotype with hypertrophic cardiomyopathy (HCM). Native T1 mapping by CMR is useful for diagnosis in cardiac amyloidosis but its prognostic potential has never been assessed.
Methods: 134 patients with wild-type ATTR (ATTRwt) (122 males, age 76±7 years), 81 patients with hereditary-type (ATTRm) (60 males, age 69±11 years), 44 patients with HCM (32 males, age 51±13 years), and 12 asymptomatic mutation carriers (4 males, age 47±10 years) were studied. All subjects underwent CMR with T1 mapping and ECV measurement. ATTR patients also underwent ^{99m}Tc-DPD scintigraphy.
Results: Native T1 and ECV were elevated in ATTR compared to HCM (p<0.001) and were both associated with a high diagnostic accuracy (area under the curve, 0.87(95% confidence interval [CI]:0.82–0.91) for T1 and of 0.91 (95%CI:0.87–0.94 for ECV). No significant difference in native T1 and ECV was found between ATTRwt and ATTRm, and ECV correlated well with ^{99m}Tc-DPD scintigraphy. During follow-up of a mean 32 ± 17 months, 55 ATTRwt and 40 ATTRm patients died. Native T1 and ECV predicted death (T1: HR 1.225 each 59ms increase; 95% CI:1.010-1.486;p<0.05 and ECV: HR 1.155 each 3% increase; 95% CI:1.097-1.216;p<0.001), but only ECV remained independently predictive after adjustment for age, N-terminal pro b-type natriuretic peptide, LV ejection fraction, E/E', LV mass index and DPD grade and LGE.
Conclusions: Native T1 mapping and ECV are good diagnostic techniques in cardiac ATTR amyloidosis that associate with prognosis. Both parameters correlate with mortality, but only ECV remains independently predictive of prognosis, suggesting that it is a more robust marker in cardiac ATTR amyloidosis.

Key words: Amyloidosis, ATTR, CMR, ECV

LIST OF ABBREVIATIONS
ATTR amyloidosis: Transthyretin amyloidosis
ATTRm: Hereditary transthyretin amyloidosis
ATTRwt: Wild-type transthyretin amyloidosis
CMR: Cardiovascular magnetic resonance
ECV: Extracellular volume fraction
HCM: Hypertrophic cardiomyopathy
LGE: Late gadolinium enhancement
LVH: Left ventricular hypertrophy
NT-proBNP: N-terminal pro-brain natriuretic peptide
^{99m}Tc-DPD: ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid

INTRODUCTION

Systemic amyloidosis is caused by deposition of insoluble amyloid fibrils in the extracellular space of tissues and organs, leading to progressive organ failure and death. More than 30 different precursor proteins have the propensity to form amyloid fibrils (1), but only two types account for most cases of cardiac amyloidosis: immunoglobulin light-chain (AL) and transthyretin (ATTR). Transthyretin-related amyloidosis, in turn, may be either hereditary (ATTRm) arising from misfolding of mutated TTR or non-hereditary, caused by misfolding of wild-type transthyretin (ATTRwt, also known as senile systemic amyloidosis). Cardiac involvement is the principal driver of prognosis in systemic amyloidosis although outcome differs markedly between types (2).

Cardiac ATTR amyloidosis is a progressive and usually fatal cause of heart failure, typically occurring in older people, for which awareness and clinical recognition have greatly increased in recent times.

Formerly, diagnosis of cardiac ATTR amyloidosis required demonstration of amyloid deposits with an endomyocardial biopsy (3) but advances in diagnostic imaging, including cardiac magnetic resonance (CMR) imaging (4,5) and re-purposed bone scintigraphy (6-9) along with blood/urine exclusion of free light chains now enable non-invasive, non-histological diagnosis of cardiac ATTR amyloidosis, which has resulted in a greater than 30-fold increase in the diagnosis of this condition in our Center during the past decade.(10)

CMR has lately emerged as a robust technique that can provide unique information about tissue composition. CMR can visualize, with late gadolinium enhancement (LGE), and measure, with T1 mapping, the continuum of cardiac amyloid deposition. T1 mapping, before the administration of contrast (4,11), can measure the intrinsic signal from the myocardium (native

myocardial T1), whilst T1 maps pre and post administration of Gadolinium-based contrast can be used to calculate the myocardial extracellular volume (ECV). Both native myocardial T1 and ECV have been extensively validated in cardiac amyloidosis as surrogate markers of infiltration. They have been shown to correlate with disease burden, detect early disease and have good diagnostic accuracy (4,11). Furthermore, in cardiac AL amyloidosis, higher T1 and ECV measurements have been shown to be associated with a shorter event free survival (12). However, in cardiac ATTR amyloidosis, although the prognostic significance of ECV has been presented,(13) neither the prognostic potential of native T1, nor the relative diagnostic accuracy or ability for native T1 versus ECV to track disease severity have been studied.

From anecdotal observation and our previous work in AL amyloidosis, we hypothesized that native myocardial T1 predicts survival in cardiac ATTR amyloidosis (12) and that there may be significant differences between the ability native T1 and ECV to track disease progression.

METHODS

Ethical approval was granted by the University College London/University College London Hospitals Joint Committees on the Ethics of Human Research Committee, and all participants provided written informed consent.

Study population

A total of 271 subjects were prospectively recruited between 2011 and 2015. The study population underwent comprehensive clinical evaluation at the National Amyloidosis Centre, London, and comprised the three groups described below. Patients were systematically followed up until June 13, 2017, the date of censoring.

ATTR amyloidosis patients: Cardiac ATTR amyloidosis was defined as the combination of symptoms with an echocardiogram consistent with or suggestive of cardiac amyloidosis, a grade

2 or 3 cardiac uptake on ^{99m}Tc-DPD scintigraphy in the absence of a monoclonal gammopathy or, in the presence of monoclonal gammopathy, a cardiac biopsy confirming ATTR (14). Possible cardiac ATTR amyloidosis was defined by grade 1 cardiac uptake on ^{99m}Tc-DPD scintigraphy in the absence of a monoclonal gammopathy.(4,13) All subjects underwent sequencing of exons 2, 3, and 4 of the *TTR* gene.

Of the 271 subjects included in this study, 198 had definitive cardiac ATTR amyloidosis (171 male, 86%; age 74 ± 8 years), 17 had possible cardiac ATTR amyloidosis (11 male, 65%; age 70 ± 14 years), 12 were *TTR* gene mutation carriers and 44 had hypertrophic cardiomyopathy.

TTR* gene mutation carriers:* Individuals with amyloidogenic *TTR* gene mutations were defined as carriers on the basis of being clinically asymptomatic, having no cardiac uptake on ^{99m}Tc-DPD scintigraphy and normal echocardiography, CMR, N-terminal proB-type natriuretic peptide (NT-proBNP) and Troponin T. Twelve *TTR* gene mutation carriers were recruited (4 male, 33%; age 47 ± 11 years).

HCM patients: There were 44 patients with HCM (32 male, 73%; 51 ± 13 years) fulfilling diagnostic criteria. Hypertrophic cardiomyopathy was defined by the presence of increased ventricular wall thickness or mass in the absence of loading conditions (hypertension, valve disease) sufficient to cause the observed abnormality.(15) In addition to the *TTR* gene carrier group described above, HCM patients constituted the non-cardiac ATTR group.

Exclusion criteria

We excluded patients with contraindications to CMR including glomerular filtration rate <30 mL/min.

CMR protocol

All participants underwent standard CMR on a 1.5T clinical scanner. A standard volumetric and LGE study was performed. The gadolinium-based contrast agent used was 0.1 mmol/kg of gadoterate meglumine (Dotarem, Guerbet S.A., France). LGE imaging was acquired using magnitude reconstruction in all patients and phase-sensitive inversion recovery reconstruction (PSIR) in 82% of patients with either standard fast low-angle shot inversion recovery or balanced steady state free precession sequence. For native and post-contrast T1 mapping, 4-chamber long-axis images were acquired using the shortened modified look-locker inversion recovery (ShMOLLI) sequence after regional shimming. (16) After a bolus of contrast and standard LGE imaging, the T1 measurement was repeated with the ShMOLLI sequence.(17)

CMR image analysis

All CMR images and maps were analysed offline. T1 measurement was performed by drawing a region of interest (ROI) in the basal to mid septum of the appropriate 4-chamber map. For ECV measurement, a single ROI was drawn in each of the 4 required areas: myocardial T1 estimates (basal to mid septum in 4 chamber map) and blood T1 estimates (LV cavity blood pool in 4 chamber map, avoiding the papillary muscles) before and after contrast administration. Hematocrit was measured in all subjects immediately before each CMR study. ECV was calculated as: myocardial ECV = (1-hematocrit) x ($\Delta R1$myocardium/$\Delta R1$blood), where R1=1/T1.

Before our adoption of PSIR for all amyloidosis patients, because myocardial nulling can be difficult in the presence of amyloid, any confusion with magnitude reconstruction images was resolved by selecting the images that most matched the post-contrast T1 maps, with "bright" LGE expected to correlate with areas of the lowest postcontrast T1 (i.e., the highest gadolinium concentration, the highest interstitial expansion).

The LGE pattern was classified into 3 groups according to the degree of transmurality: group 1, no LGE; group 2, subendocardial LGE (when there was global subendocardial but no transmural LGE); and group 3, transmural LGE (when the LGE was extending transmurally). A scan was classified by the most extensive LGE identified. Thus, a patient with basal transmural LGE but apical subendocardial LGE would be classified as transmural.(5)

^{99m}Tc-DPD Scintigraphy

Subjects were scanned using hybrid single-photon emission computed tomography (SPECT) computed tomography (CT) gamma cameras following administration of 700 MBq of intravenously-injected ^{99m}Tc-DPD. Whole-body planar images were acquired after 3 h, followed by SPECT of the heart coupled with a low-dose, noncontrast CT scan.(18) Gated and nongated cardiac SPECT reconstruction and SPECT-CT image fusion was performed on the Xeleris workstation (GE Healthcare, Wauwatosa, Wisconsin). Cardiac retention of ^{99m}Tc-DPD was scored visually according to the grading devised by Perugini et al. (6) using the following grading system: grade 0, absent cardiac uptake; grade 1, mild cardiac uptake less than bone; grade 2, moderate cardiac uptake equal or greater than bone; and grade 3, intense cardiac uptake associated with substantial reduction or loss of bone signal. Uptake was verified by visual review of SPECT imaging.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM, Armonk, New York). All continuous variables were normally distributed (Shapiro-Wilk test), other than NT-proBNP, which was natural log transformed for bivariate testing. These are presented as mean $\pm$ SD with untransformed NT-proBNP presented as median and interquartile range. Comparisons between multiple groups were performed by 1-way analysis of variance with post hoc Bonferroni

correction. The chi-square test or Fisher exact test was used to compare categorical data as appropriate. Correlations between parameters were assessed using Pearson (r) or Spearman's rho. Receiver-operating characteristic (ROC) curve analysis was performed to define the diagnostic accuracy of native T1 and ECV. The AUCs were compared statistically for correlated ROC curves with DeLong method.

Survival was evaluated using Cox proportional hazards regression analysis, providing estimated hazard ratios (HR) with 95% confidence intervals (CI) and Kaplan-Meier curves. All variables were first explored with univariate Cox regression. Separate multivariate models evaluated the independent predictive value of T1 and ECV above other clinically and statistically significant covariates. Statistical significance was defined as $p < 0.05$.

RESULTS

The details of the 271 subjects are shown in table 1. A total of 198 patients with definitive ATTR amyloidosis, 17 patients with possible ATTR amyloidosis and 12 mutation carriers were enrolled. These subjects were compared with 44 patients with HCM.

Of the patients with definitive ATTR, 125 had wild-type ATTR and 73 hereditary ATTR (ATTRm); the TTR mutations were V122I (n = 40); T60A (n = 20); V30M (n = 5); and S77Y, E54G, E54L, E89K, D38Y, F44L, G89L and L12P in one case each. Among 17 patients with suspected cardiac ATTR (DPD grade 1 one DPD scintigraphy), 9 had wild-type TTR gene sequence and 8 had amyloidogenic TTR gene mutations comprising S77Y (n = 3) and V30M, I107F, E54G, G47V, and I84S in 1 case each. The variants present in mutation carriers were T60A (n = 6); V30M (n = 5); and S77Y (n = 1).

Correlation between T1 and ECV

Native T1 and ECV have a good correlation (R = 0.726) in all ATTR subjects and this correlation remained good in low ECV values (R = 0.735 in ECV< 0.40). However, this correlation was significantly worse when high ECV values were analysed (R = 0.351 in ECV ≥ 0.40). (Figure 1 and 2) Native T1 and ECV have also a good correlation in HCM patients (R=0.684).

T1 and ECV diagnostic accuracy

As predicted, T1 and ECV were elevated in ATTR patients compared with HCM and mutation carriers (native T1: 1096 ± 51ms vs 1013 ± 64ms, p<0.001; ECV: 0.61 ± 0.12 vs 0.36 ± 0.13, p<0.001).

The ROC curve analysis was performed for the discrimination of definitive cardiac ATTR amyloidosis or possible cardiac ATTR amyloidosis from the combined differential diagnoses of HCM or ATTR mutation carriers without evidence of cardiac amyloidosis.

The combined group of definitive ATTR and possible ATTR patients had an area under the ROC curve (AUC) of 0.87 (95% confidence interval [CI]: 0.82 – 0.91) for T1 and 0.91 (95% confidence interval [CI]: 0.87 – 0.94) for ECV. The T1 cut-off value to diagnose definitive or possible cardiac ATTR was 1048ms with a specificity of 80.36% and sensitivity of 86.54% and for ECV was 0.469 with a specificity of 82.14% and sensitivity of 92.46%

When a subgroup analysis was performed according the ATTR aetiology (ATTRm, ATTRwt) diagnostic accuracy remained similarly good. The AUC for T1 in ATTRm was 0.88 (95% confidence interval [CI]: 0.82 – 0.93) compared with an AUC for ECV of 0.92 (95% confidence interval [CI]: 0.87 – 0.96). T1 and ECV had also similar diagnostic accuracy in ATTRwt patients: T1 AUC was 0.86 (95% confidence interval [CI]: 0.80 – 0.90) and ECV AUC of 0.90 (95% confidence interval [CI]: 0.85 – 0.94). (Figure 3) The T1 cut-off value to diagnose

definitive or possible cardiac ATTRm was 1051ms with a specificity of 82.14% and sensitivity of 86.08% and 0.469 for ECV with a specificity of 82.14% and sensitivity of 91.89%. The T1 cut-off value to diagnose definitive or possible cardiac ATTRwt was 1048ms with a specificity of 80.36% and sensitivity of 86.05% and 0.469 for ECV with a specificity of 82.14% and sensitivity of 92.80%.

There were no statistically significant differences in the AUC for native T1 and ECV in all subgroup comparisons.

T1, ECV and DPD/LGE findings, cardiac function, biomarkers and 6-min walk test

Both native T1 and ECV increased with increasing cardiac uptake as assessed by bone scintigraphy ($p < 0.001$ for trend). Native T1 and ECV were not elevated in mutation carriers (native T1: 968 ± 41ms; ECV 0.29 ± 0.03) but were elevated in the 17 patients with possible ATTR (DPD grade 1) (native T1: 1023 ± 64ms, ECV: 0.41 ± 0.13, $p < 0.05$ for both), all of which had no amyloid-like LGE by CMR, with the exception of patients with the Se77Tyr variant. (Figure 4)

Native T1 and ECV values were also elevated in HCM patients compared to ATTR mutation carriers (native T1 1026 ± 64ms, ECV 0.38 ± 0.15, $p<0.05$ for both).

Correlations were broadly similar for T1 and ECV across ATTR types (table 2), but ECV correlated more strongly with parameters of cardiac function, biomarkers and 6 minute walking test than T1. Overall in all ATTR patients, T1 and ECV correlated with indexes of systolic and diastolic function, indexed LV mass, and known prognostic biomarkers as well as functional markers (6-minute walk test performance) in keeping with our previous findings (4,11,12). Furthermore, ECV correlated with indexed stroke volume but T1 did not.

For subgroup analyses (ATTRm and ATTRwt), correlations were lower, reflecting the smaller sample sizes.

In asymptomatic ATTR mutations carriers, there were no statistically significant correlations.

Association between T1, ECV and outcome

At follow-up (mean 32 ± 17 months), 95 of 227 (42%) subjects had died (55 with wild-type ATTR and 40 with ATTRm). Native T1 and ECV predicted death in the ATTR population (T1: HR 1.225 each 59ms increase; 95% confidence interval, 1.010-1.486; p<0.05 and ECV: HR, 1.155 each 3% increase; 95% confidence interval, 1.097-1.216; p<0.001), and ECV also predicted death separately in the wild-type ATTR and ATTRm groups (p<0.01 for both). However, native T1 was not predictive of death when wild-type ATTR and ATTRm groups were analysed separately. (Figure 5)

ECV remained significantly associated with mortality (HR: 1.101; 95% CI: 1.022 to 1.187; p < 0.05) in multivariate Cox models that included age, NT-proBNP, LV ejection fraction, E/E', LV mass index and DPD grade. Only age, ECV and NTproBNP remained significantly associated with mortality when LGE was added to the multivariate model (ECV, HR: 1.106 each 3% increase; 95% CI: 1.011-1.209; p < 0.05; LGE, HR 0.868; 95% CI: 0.447-1.973; p=0.939). In contrast, native T1 didn't remain significantly associated with mortality after adjustment for age, NT-proBNP, LV ejection fraction, E/E', LV mass index and DPD grade (p=0.971). Native T1 remained not significant after the addition of LGE to the model (p = 0.729).

DISCUSSION

In this large ATTR amyloidosis population, we describe for the first time that native T1 mapping and ECV are good diagnostic techniques in cardiac ATTR amyloidosis, however in high levels of infiltration, native T1 and ECV can be discordant. Both parameters also correlate with

mortality in cardiac ATTR amyloidosis. Nevertheless, only ECV remains independently predictive of prognosis, suggesting that it is a more robust marker in cardiac ATTR amyloidosis. (Supplement table 1 and 2) In addition, we demonstrate that non-diagnostic DPD uptake (grade 1), previously held to be indeterminate but inconsistent with definitive ATTR amyloidosis, is associated with abnormal myocardial T1 and ECV, suggesting that CMR can detect a phenotype of early amyloid infiltration.

Native T1 and ECV have lately emerged as the first non-invasive quantitative markers of myocardial amyloid infiltration. Our earlier work in ATTR amyloidosis demonstrated that elevated native myocardial T1 in cardiac ATTR amyloidosis, was more sensitive than LGE imaging and had high diagnostic accuracy. Similarly, ECV was also elevated in patients with early stage disease when conventional clinical testing and LGE were normal, it tracked a range of markers of disease severity and correlated with prognosis in ATTR amyloidosis.(13) Whilst initial studies suggested the two biomarkers had similar clinical implications, important differences have recently emerged between the two main types of cardiac amyloidosis, with native T1 being relatively higher in AL amyloidosis compared to ATTR, and vice versa for ECV.(19) The present study extends these intriguing observations, demonstrating that native T1 correlated with prognosis in ATTR amyloidosis and highlighting differences between the two biomarkers in ATTR amyloidosis, where both native T1 and ECV show a similar diagnostic accuracy, but ECV has significantly better correlation with all markers of amyloid burden and better prognostic power than native T1. We also demonstrate a good correlation between ECV and native T1 for low level of infiltration but very poor correlation when amyloid burden is moderate or severe.

We believe that these differences represent different biological information provided by native T1 and ECV measurements. Cardiac amyloidosis is emerging as a spectrum characterized by variable degrees of amyloid infiltration, myocardial edema, inflammation and differential myocyte response with myocyte hypertrophy. The administration of contrast and ECV measurements enables us to isolate the signal from the extracellular space, but native myocardial T1 provides a composite signal from the intra and extracellular spaces, a signal potentially influenced by other pathophysiological mechanisms beyond simple amyloid load. Native myocardial T1 is highly influenced by water content in the tissue and will therefore be significantly raised by the presence of myocardial edema.(20) There are two types of myocardial edema: intracellular and extracellular. ECV is elevated when there is extracellular edema and T1 is elevated in both types.(21) Myocardial edema therefore influences both native T1 and ECV, however this influence is disproportionate when the edema is mainly intracellular, with the degree of elevation being higher in native T1 than in ECV. On the other hand, a relative increase in myocyte hypertrophy compared to amyloid burden will likely decrease the native T1.

In cardiac ATTR amyloidosis, progressive amyloid deposition is thought to be the main driver of disease progression, whilst in AL amyloidosis light chain toxicity or rate of amyloid deposition are believed to also play an important role, especially in contributing to early mortality. In this context, the better correlation of ECV not only with markers of disease severity but also prognosis in ATTR amyloidosis is not surprising, but in keeping with the hypothesis of ECV being a better marker of amyloid deposition. This hypothesis is also in line with the different significance of native T1 in AL amyloidosis as a powerful independent predictor of prognosis, since the ability to track both amyloid load and associated myocardial edema is important in this particular amyloid subtype.

From this study, different roles emerge for measurements of native T1 and ECV in ATTR amyloidosis. The similar diagnostic performance supports the use of native T1 for diagnosis of ATTR amyloidosis, which also has the significant advantage of being a non-contrast technique. Lack of requirement for contrast means that native myocardial T1 mapping can be performed in patients with advanced renal failure, in whom administration of contrast is contraindicated. However, in this study we excluded patients with severe renal impairment leaving a knowledge gap on the clinical utility on non-contrast CMR in this setting. Lack of need to give contrast is also attractive in the general population given reduced cost and recent potential concerns about gadolinium accumulating in the brain, even though this has not been demonstrated for the cyclic gadolinium agents, such as that used in this study.(22) On the other hand, ECV is a better marker in ATTR amyloidosis for risk stratification and probably for tracking disease progression. These differences are also supported and at least in part explained by the relationship between native T1 and ECV. There is a good correlation between native T1 and ECV up to and ECV of 0.4, but when the extracellular volume expansion is higher the correlation between the two measurements becomes poor. The inability of native T1 to track increasing amyloid burden when the ECV is greater than 0.4 is likely to represent the main reason for the worse prognostic performance on native myocardial T1 compared to ECV. Both biomarkers do increase in subclinical disease, supporting their equivalent role as diagnostic markers, as confirmed by similar AUCs in the ROC curve analysis.

Study limitations. Cardiac biopsy was available in only a minority of patients, but this cohort of patients was fully characterized using the validated and now widely used non-invasive criteria for ATTR. (14) Patients with pacemakers or defibrillators were also excluded. A wide range of TTR mutations were included in the analysis. In this study, T1 measurements were performed by

drawing a ROI in the basal to mid septum of the appropriate 4-chamber map and the same approach was used for ECV measurements, therefore the total extent of cardiac amyloid infiltration was not assessed. T2 maps were not acquired in this study, limiting the possibility of exploring the hypothesis of myocardial edema as a potential mechanism for the increase in T1. Finally, this was a single center study where one T1 mapping technique was used. Care must be taken with interpretation of the different T1 cut-offs as T1 varies with magnetic field strength, different sequences and thus establishment of normal ranges for a given system, with use of standardization tools, is recommended.

CONCLUSION

CMR-determined native myocardial T1 and ECV provide excellent diagnostic accuracy for identification of ATTR cardiac amyloidosis and both variables track cardiac uptake on DPD scintigraphy well. Native T1 and ECV predict survival in ATTR amyloidosis, however ECV is a more robust predictor. ECV, a non-invasive quantification of the cardiac amyloid burden, remained an independent predictor of prognosis after adjustment for known prognostic factors and provide unique insight into tissue composition in cardiac amyloidosis.

Clinical Perspectives

Competency in Medical Knowledge: Native myocardial T1 and ECV have similar diagnostic accuracy identifying ATTR amyloidosis and both correlate with mortality. However, ECV is a more robust prognostic predictor, remaining independent predictor of prognosis after adjustment for knowing prognostic factor.

Translational outlook: Future studies in cardiac amyloidosis by CMR with T2 mapping could help to identify differences in amyloid biology in the main two types of cardiac amyloidosis (AL and ATTR).

References:

1.   Sipe JD, Benson MD, Buxbaum JN et al. Nomenclature 2014: Amyloid fibril proteins and clinical classification of the amyloidosis. Amyloid 2014;21:221-4.

2.   Rapezzi C, Merlini G, Quarta CC et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. Circulation 2009;120:1203-12.

3.   Pepys MB. Amyloidosis. Annu Rev Med 2006;57:223-41.

4.   Fontana M, Banypersad SM, Treibel TA et al. Native T1 mapping in transthyretin amyloidosis. JACC Cardiovasc Imaging 2014;7:157-65.

5.   Fontana M, Pica S, Reant P et al. Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. Circulation 2015;132:1570-9.

6.   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;46:1076-84.

7.   Rapezzi C, Quarta CC, Guidalotti PL et al. Usefulness and limitations of 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy in the aetiological diagnosis of amyloidotic cardiomyopathy. Eur J Nucl Med Mol Imaging 2011;38:470-8.

8.   Glaudemans AW, van Rheenen RW, van den Berg MP et al. Bone scintigraphy with (99m)technetium-hydroxymethylene diphosphonate allows early diagnosis of cardiac involvement in patients with transthyretin-derived systemic amyloidosis. Amyloid 2014;21:35-44.

9.   Maurer MS. Noninvasive Identification of ATTRwt Cardiac Amyloid: The Re-emergence of Nuclear Cardiology. Am J Med 2015;128:1275-80.

10.   Gillmore JD, Damy T, Fontana M et al. A new staging system for cardiac transthyretin amyloidosis. Eur Heart J 2017.

11.   Karamitsos TD, Piechnik SK, Banypersad SM et al. Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis. JACC Cardiovasc Imaging 2013;6:488-97.

12. Banypersad SM, Fontana M, Maestrini V et al. T1 mapping and survival in systemic light-chain amyloidosis. Eur Heart J 2015;36:244-51.

13. Martinez-Naharro A, Treibel TA, Abdel-Gadir A et al. Magnetic Resonance in Transthyretin Cardiac Amyloidosis. J Am Coll Cardiol 2017;70:466-477.

14. Gillmore JD, Maurer MS, Falk RH et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation 2016;133:2404-12.

15. Elliott P, Andersson B, Arbustini E et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008;29:270-6.

16. Fontana M, White SK, Banypersad SM et al. Comparison of T1 mapping techniques for ECV quantification. Histological validation and reproducibility of ShMOLLI versus multibreath-hold T1 quantification equilibrium contrast CMR. J Cardiovasc Magn Reson 2012;14:88.

17. White SK, Sado DM, Fontana M et al. T1 mapping for myocardial extracellular volume measurement by CMR: bolus only versus primed infusion technique. JACC Cardiovasc Imaging 2013;6:955-62.

18. 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;15:1289-98.

19. Fontana M, Banypersad SM, Treibel TA et al. Differential Myocyte Responses in Patients with Cardiac Transthyretin Amyloidosis and Light-Chain Amyloidosis: A Cardiac MR Imaging Study. Radiology 2015;277:388-97.

20. Kotecha T, Martinez-Naharro A, Treibel TA et al. Multiparametric Mapping to Understand Pathophysiology in Cardiac Amyloidosis. Heart 2017;103:A1-A2.

21. Messroghli DR, Moon JC, Ferreira VM et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by

the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European

Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson 2017;19:75.

22.   McDonald RJ, McDonald JS, Kallmes DF et al. Gadolinium Deposition in Human Brain Tissues

after Contrast-enhanced MR Imaging in Adult Patients without Intracranial Abnormalities.

Radiology 2017;285:546-554.

Figure 1. Correlation between native T1 and ECV in ATTR amyloidosis. Correlation between native T1 and ECV, ECV < 0.40 (blue) and ECV ≥ 0.40 (red).
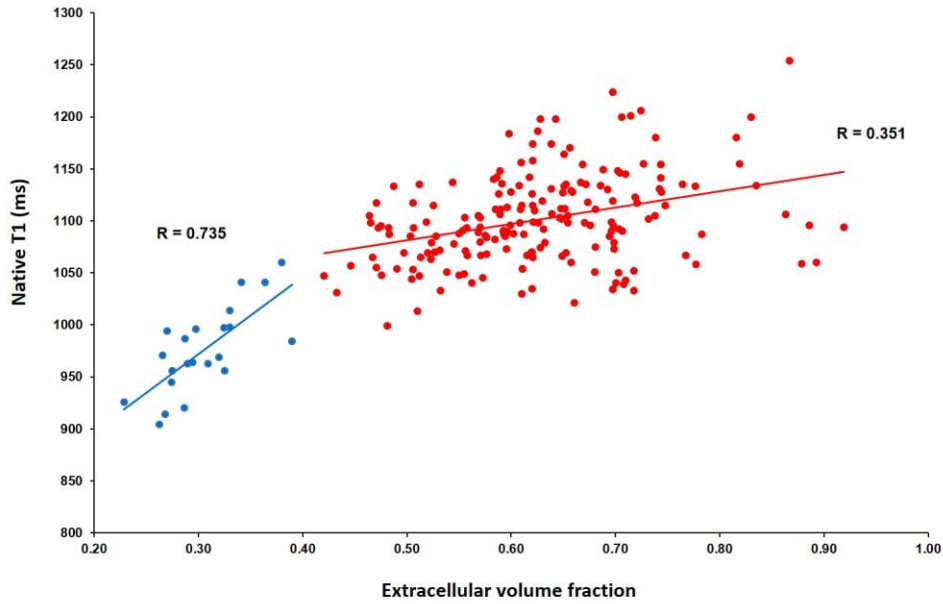
Figure 2. Native T1, LGE and ECV in ATTR amyloidosis. Short axis SSFP cine (right panel); corresponding native T1 maps, PSIR LGE and ECV maps of three subjects; showing (top panel) normal T1, transmural LGE, and very elevated ECV values in cardiac ATTR amyloidosis, (middle panel) very high T1 values, transmural LGE and high ECV values in another cardiac ATTR amyloidosis; and (bottom panel) normal T1, no LGE and normal ECV in a normal heart. Both patients (top and middle panel) have high ECV and transmural LGE but discordant T1 (normal at the top and very elevated in the middle).
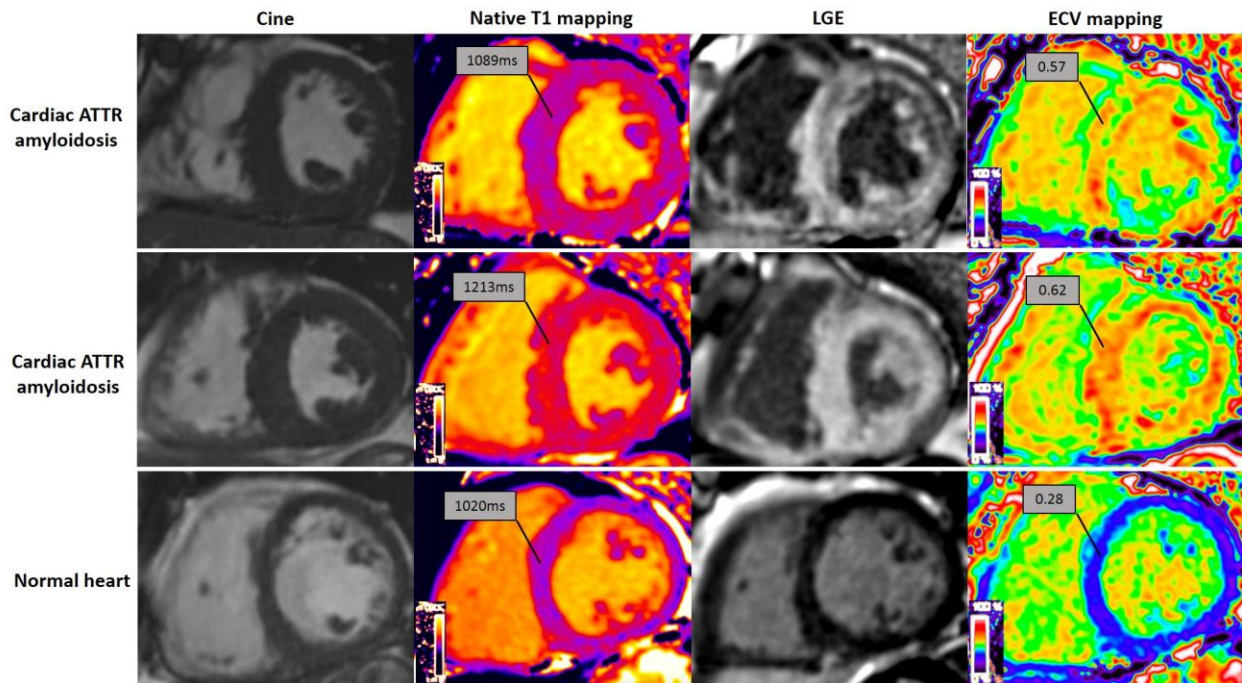
Figure 3. Receiver operative characteristic curve (ROC) for discrimination of possible or definite cardiac amyloid by native T1 and ECV from the combined HCM or ATTR mutation carriers. ROC curve for discrimination of possible or definite cardiac amyloid by native myocardial T1 (blue) and ECV (green) from the clinically significant combined differential diagnosis of HCM or ATTR mutation carriers without evidence of cardiac amyloid for: (A) all ATTR amyloid patients; (B) hereditary-type ATTR amyloid; or (C) wild-type ATTR. AUC= area under the curve; CI = confidence interval.

ATTR: all	Native T1	ECV
AUC	0.87	0.91
CI	0.82-0.91	0.87-0.94
P-value	< 0.001	< 0.001

ATTRm	Native T1	ECV
AUC	0.88	0.92
CI	0.82-0.93	0.87-0.96
P-value	< 0.001	< 0.001

ATTRwt	Native T1	ECV
AUC	0.86	0.90
CI	0.80-0.90	0.85-0.94
P-value	< 0.001	< 0.001
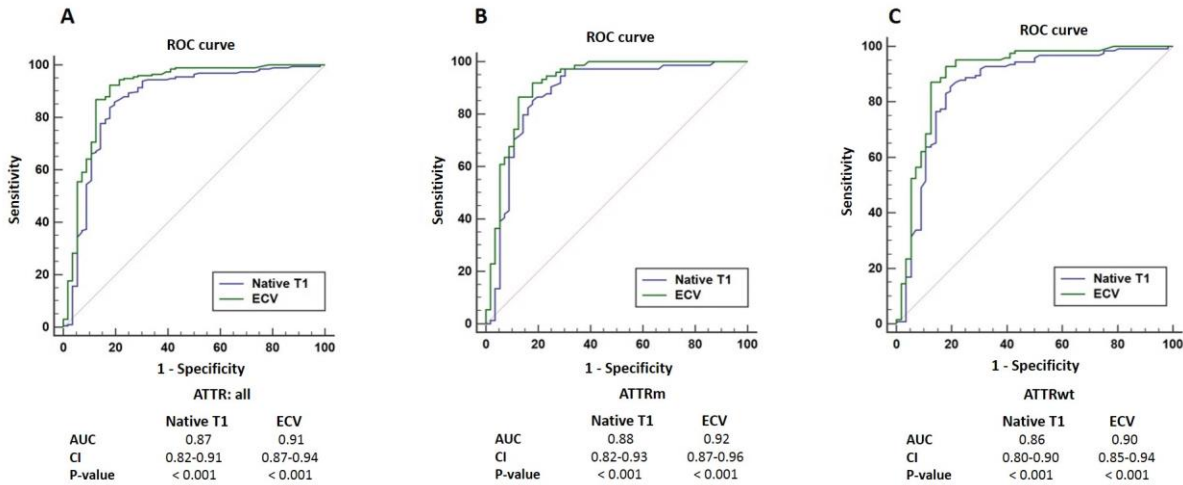
Figure 4. **DPD grade vs native T1 and ECV.** DPD grade vs mean native myocardial T1 (left panel) and ECV (right panel) $\pm$ 2 SE in gene carriers and ATTR patients according to different degrees of uptake on the ^{99m}Tc-DPD scintigraphy. P for trend < 0.001 for both.
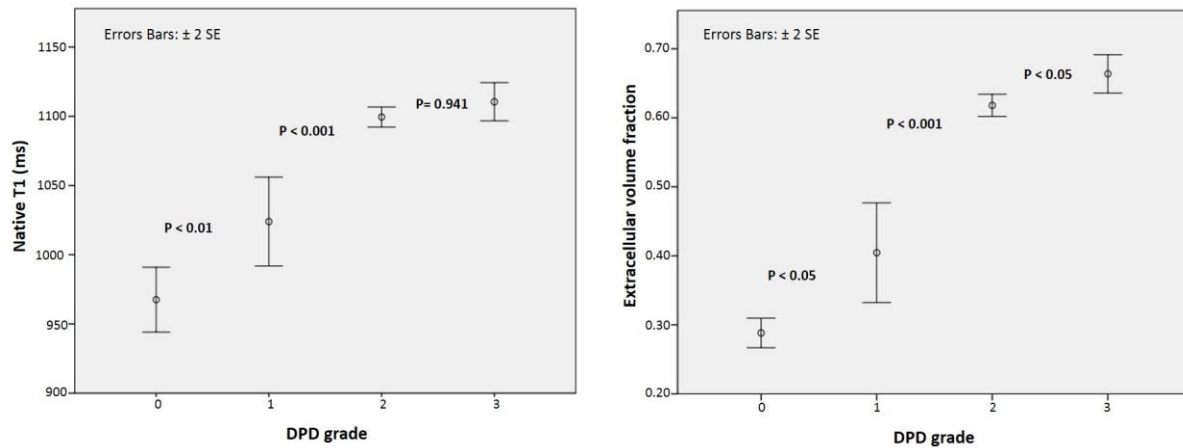
Figure 5. Kaplan-Meier curves for ECV and native T1. Native T1 (top panel) was correlated with mortality in all patients with cardiac transthyretin amyloidosis (ATTR) (left panel), but it was not correlated with mortality when the analysis was performed in hereditary and wild-type ATTR (middle and right panels). ECV (bottom panel) was correlated with mortality in all patients with cardiac transthyretin amyloidosis (ATTR) (left panel), as well as in hereditary and wild-type ATTR (middle and right panels).
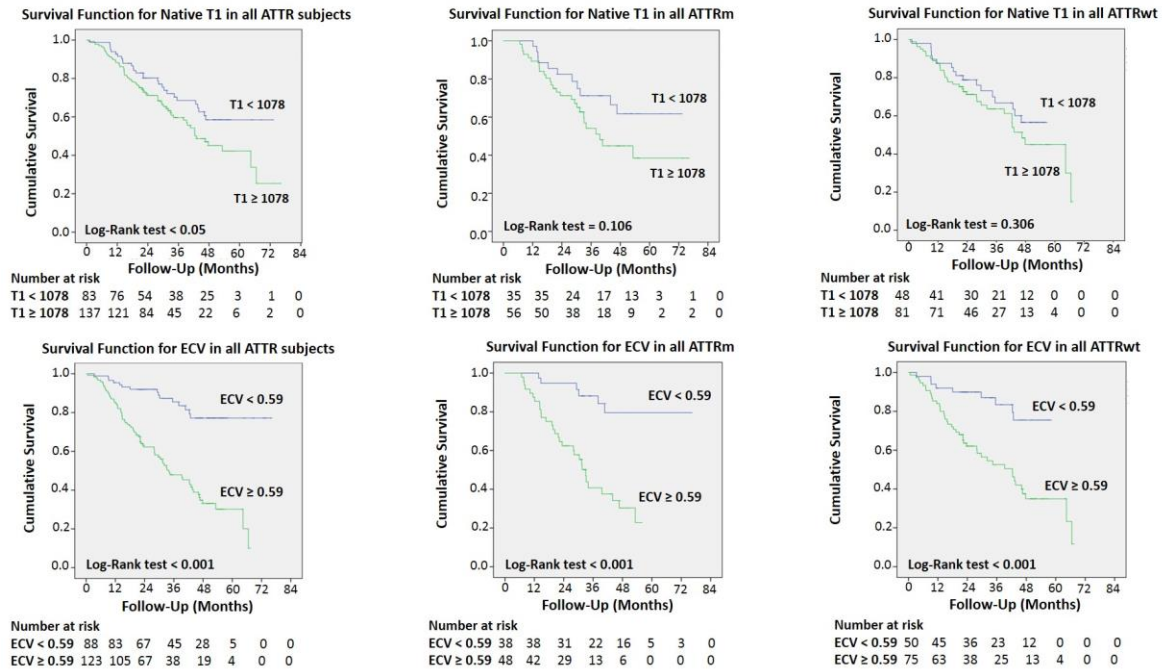
Table 1. Biomarkers, echocardiographic parameters and CMR findings in patients with ATTR amyloidosis and mutation carriers.

	All ATTR patients (n = 227)	ATTRwt (n = 134)	ATTRm (n = 81)	ATTR Mutation Carriers (n = 12)
Age, years	72 ± 11	76 ± 7	69 ± 10	47 ± 11
Biomarkers				
NT-proBNP, ng/L	286 (142 – 538)	322 (179 – 518)	258 (126 – 614)	6 (3 – 8)
6 min WT	318 ± 143	313 ± 134	290 ± 142	521 ± 49
Echocardiographic Parameters				
IVS, cm	1.59 ± 0.28	1.64 ± 0.24	1.61 ± 0.25	0.95 ± 0.12
LA area, cm^2	25.65 ± 6.57	26.66 ± 6.05	25.46 ± 6.31	15.10 ± 5.35
E-wave, cm/s	0.83 ± 0.20	0.84 ± 0.19	0.82 ± 0.21	0.79 ± 0.12
A-wave, cm/s	0.49 ± 0.24	0.48 ± 0.24	0.48 ± 0.23	0.67 ± 0.17
E/A	3.14 ± 8.71	3.16 ± 6.48	3.50 ± 12.12	1.23 ± 0.25
Average E', cm/s	0.11 ± 0.78	0.06 ± 0.02	0.20 ± 1.30	0.1 ± 0.05
E/E'	16 ± 7	16 ± 6	17 ± 7	13 ± 18
E-wave deceleration time, ms	178 ± 54	179 ± 55	177 ± 54	181 ± 48
2D GLS	-11.7 ± 4.9	-11.4 ± 4.5	-11.3 ± 5.0	-18.8 ± 3.4
CMR parameters				

LV mass, g	241 ± 77	255 ± 72	238 ± 72	114 ± 37
LV mass$_i$, g/cm^2	129 ± 41	134 ± 37	132 ± 40	59 ± 12
Maximal IVS, mm	19 ± 5	20 ± 4	19 ± 4	9 ± 2
LVEDV, mL	134 ± 36	137 ± 37	130 ± 35	124 ± 25
LVEDV$_i$, mL/m^2	71 ± 18	71 ± 19	71 ± 17	66 ± 13
LVESV, mL	62 ± 31	63 ± 32	64 ± 30	39 ± 12
LVESV$_i$, mL/m^2	32 ± 16	32 ± 16	35 ± 16	20 ± 6
LVSV, mL	72 ± 20	74 ± 20	67 ± 21	85 ± 16
LVSV$_i$, mL/m^2	38 ± 10	38 ± 10	37 ± 10	45 ± 8
LVEF, %	56 ± 14	56 ± 14	53 ± 15	69 ± 5
RVEDV, mL	132 ± 38	134 ± 37	130 ± 42	125 ± 27
RVEDV$_i$, mL/m^2	70 ± 19	70 ± 19	71 ± 20	68 ± 14
RVESV, mL	63 ± 31	64 ± 31	65 ± 34	43 ± 11
RVESV$_i$, mL/m^2	34 ± 16	34 ± 16	35 ± 18	23 ± 6
RVSV, mL	68 ± 20	70 ± 19	63 ± 19	82 ± 17
RVSV$_i$, mL/m^2	36 ± 10	36 ± 10	34 ± 9	44 ± 9
RVEF, %	53 ± 13	54 ± 13	51 ± 14	66 ± 4
LA area, cm^2	31 ± 9	33 ± 11	30 ± 6	22 ± 4
RA area, cm^2	28 ± 8	30 ± 8	28 ± 8	19 ± 2
MAPSE, mm	8 ± 3	8 ± 3	7 ± 3	14 ± 2
TAPSE, mm	13 ± 5	13 ± 5	13 ± 5	23 ± 3

LGE (none/subendocardial/transmural), %	11/23/66	6/25/69	5/24/71	100/0/0
ECV, %	56 ± 16	60 ± 11	63 ± 13	29 ± 3
Native Myocardial T1, ms	1079± 64	1092 ± 51	1104 ± 49	968 ± 41

Values are mean ± SD, %, or median (interquartile range). ATTR = transthyretin amyloidosis; CMR = cardiac magnetic resonance; ECV = extracellular volume; GLS = global longitudinal strain; IVS = interventricular septum; LA = left atrium; LPW = left posterior wall; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; LVSV = left ventricular stroke volume; MAPSE = mitral annular plane systolic excursion; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RA = right atrium; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; RVSV = right ventricular stroke volume; TAPSE = tricuspid annular plane systolic excursion.

Table 2. Correlations between T1 and ECV and Cardiac Function, Biomarkers and 6-minute walk test in ATTR patients.

	All ATTR (n=227)		ATTRm (n=81)		ATTRwt (n=134)		Mutation carriers (n=12)	
	T1	ECV	T1	ECV	T1	ECV	T1	ECV
CMR parameters								
LV mass$_i$, g/m^2	**0.537***	**0.619***	**0.356***	**0.504***	**0.483***	**0.535***	-0.188	-0.428
LA area$_i$, cm^2/m^2	**0.244***	**0.403***	-0.004	**0.267†**	**0.179†**	**0.319***	-0.159	0.222
LVEF, %	**-0.273***	**-0.567***	-0.015	**-0.625***	**-0.301***	**-0.466***	0.550	0.479
SV$_i$, ml/m^2	-0.115	**-0.402***	**0.247†**	**-0.460***	**-0.184†**	**-0.304***	-0.198	-0.076
Echocardiographic parameters								
E/E'	**0.277***	**0.306***	**0.238†**	**0.324***	**0.241***	**0.313***	0.540	**0.679†**
E-wave deceleration time, ms	-0.006	**-0.149†**	-0.077	**-0.260†**	0.072	-0.112	-0.402	-0.158
2-dimensional GLS, %	**-0.461***	**-0.671***	**-0.397***	**-0.699***	**-0.374***	**-0.574***	0.355	0.147
6 minute walk test								
6-minute walk test, m	**-0.246***	**-0.341***	-0.051	-0.051	-0.071	**-0.233†**	0.271	0.235
Biomarkers								
NT-proBNP, pmol/l	**0.482***	**0.731***	0.210	**0.648***	**0.338***	**0.597***	-0.184	-0.038
Troponin T, pmol/l	**0.462***	**0.618***	0.022	**0.340†**	0.200	**0.458***	0.326	-0.179

Values are Pearson's r correlation coefficient. *p< 0.01 †p<0.05

GLS = global longitudinal strain; LV= left ventricle; LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-brain natriuretic peptide; SV_i = stroke volume indexed.