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SHORT REPORT

Left ventricular wall thickness and severity of cardiac disease in women and men with transthyretin amyloidosis

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Aims Cardiac amyloidosis (CA) is due to a deposition of amyloid fibrils in the heart causing an increase in wall thickness. A left ventricular (LV) wall thickness ≥12 mm plus at least one red flag should raise the suspicion of CA. As normal values of LV wall thickness are lower in women, the adoption or the same cut-off values for men and women could lead to underdiagnosis or delayed diagnosis in women. We investigated the relationship between LV wall thickness and the severity of cardiac involvement in women and men with transthyretin (ATTR) CA.

Methods and results We evaluated 330 consecutive patients diagnosed with ATTR-CA at three centres (Pisa, $n = 232$; Brescia, $n = 69$; Trieste, $n = 29$). Interventricular septum (IVS) and posterior wall (PW) thickness values were lower in women ($n = 53$, 16%) than men, but most differences were abolished when indexing by body surface area (BSA), height, or height$^{2.7}$, suggesting similar disease severity when accounting for the smaller body size of women. PW thickness indexed for height$^{2.7}$ was even higher in women. We also searched for correlations between IVS and PW thickness and other indicators of the severity of cardiac disease. IVS values indexed by height$^{2.7}$ displayed tighter associations with N-terminal pro-B-type natriuretic peptide values than non-indexed IVS values. Similarly, indexed values displayed closer relationships with relative wall thickness, E/e' ratio, and tricuspid annular plane systolic excursion.

Conclusions Indexed LV wall thickness values, particularly by height$^{2.7}$, reflect more accurately the severity of cardiac involvement than non-indexed values.

Keywords Amyloidosis • Transthyretin • Gender differences • Wall thickness • Cut-off • Diagnosis

Background

Cardiac amyloidosis (CA) is due to a deposition of amyloid fibrils in the heart causing an increase in wall thickness. Amyloid transthyretin (ATTR) CA was traditionally considered as a disease with a much higher prevalence and a worse phenotype in men. This notion has recently been challenged, and attributed partially to the lack of indexation of echocardiographic measures,[1] starting from the diagnostic algorithm for CA. According to a European Society of Cardiology (ESC) position statement, a left ventricular (LV) wall

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Table 1 Patient characteristics

Variable	Women (n = 53, 16%)	Men (n = 277, 84%)	p-value
ATTRwt, n (%)	51 (96)	270 (98)	0.610
Age (years)	84 (80–85)	80 (76–85)	**0.006**
Height (m)	1.62 (1.60–1.65)	1.72 (1.68–1.78)	**<0.001**
BSA (m^2)	1.77 (1.69–1.85)	1.90 (1.80–2.00)	**<0.001**
Hypertension, n (%)	38 (72)	182 (66)	0.415
Diabetes, n (%)	12 (23)	51 (19)	0.480
History of CAD, n (%)	9 (17)	69 (25)	0.204
NYHA class III–IV, n (%)	20 (39)	85 (32)	0.343
NT-proBNP (ng/L)	2779 (1044–5467)	2766 (1418–5821)	0.856
hs-TnT (ng/L)	54 (30–86)	57 (39–82)	0.559
eGFR (ml/min/1.73 m^2)	46 (37–65)	60 (46–75)	**<0.001**
Gillmore stage 1, 2, 3, n (%)	16, 12, 15 (37, 28, 35)	98, 89, 32 (45, 41, 15)	**0.006**
LVEF (%)	53 (44–60)	50 (43–55)	**0.020**
GLS (%)	−12.8 (−15.0 to −8.4)	−11.3 (−15.3 to −8.4)	0.622
RWT	0.65 (0.49–0.75)	0.62 (0.53–0.75)	0.929
E/e'	16 (13–22)	16 (13–20)	0.887
LAVI (ml/m^2)	43 (35–52)	45 (37–54)	0.214
TAPSE (mm)	16 (13–20)	16 (14–19)	0.781
PAPs (mmHg)	42 (34–46)	41 (35–47)	0.930

Values are given as median (interquartile range) unless otherwise indicated.
Gillmore stages were calculated in patients with available NT-proBNP and eGFR data (n = 43 women, n = 219 men).
ATTRwt, wild-type amyloid transthyretin amyloidosis; BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; hs-TnT, high-sensitivity troponin T; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAPs, systolic pulmonary artery pressure; RWT, relative wall thickness; TAPSE, tricuspid annular plane systolic excursion.

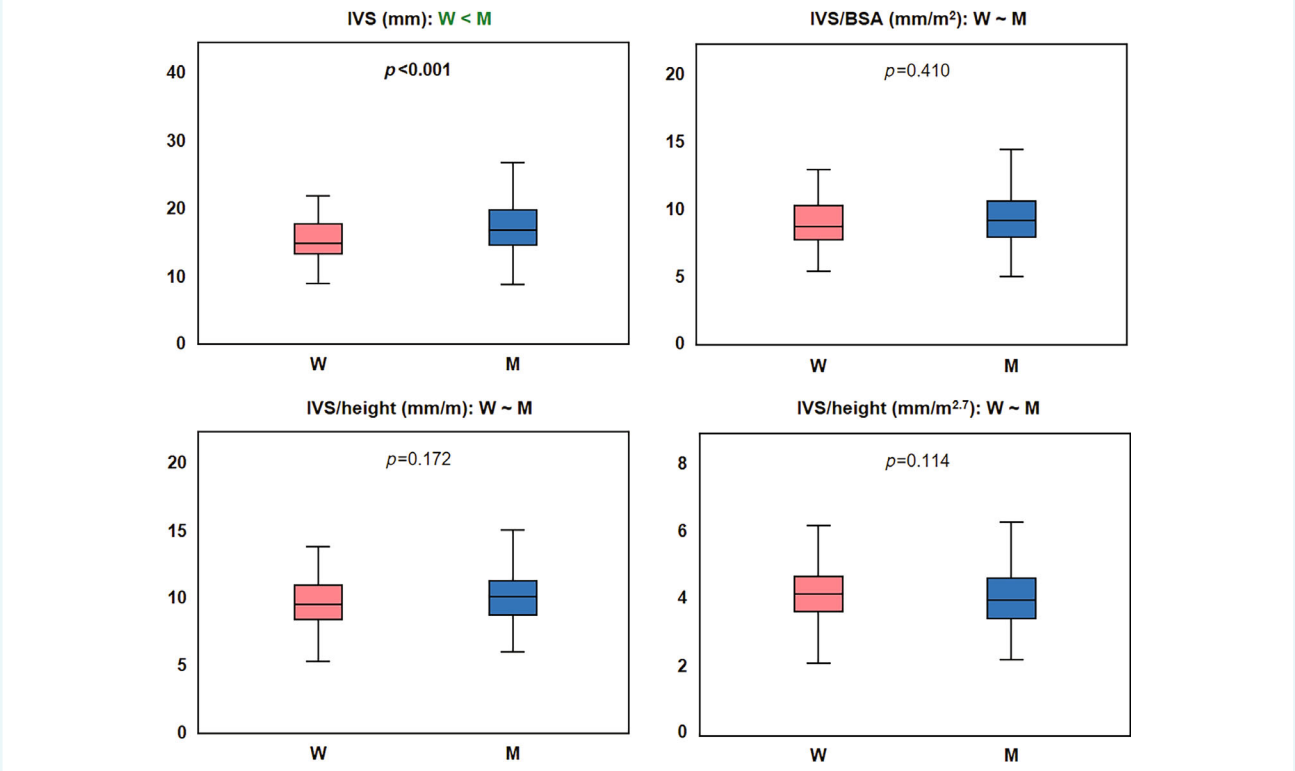

Figure 1 Indexed and not indexed values of interventricular septal thickness in women and men. BSA, body surface area; IVS, interventricular septum; M, men; W, women.

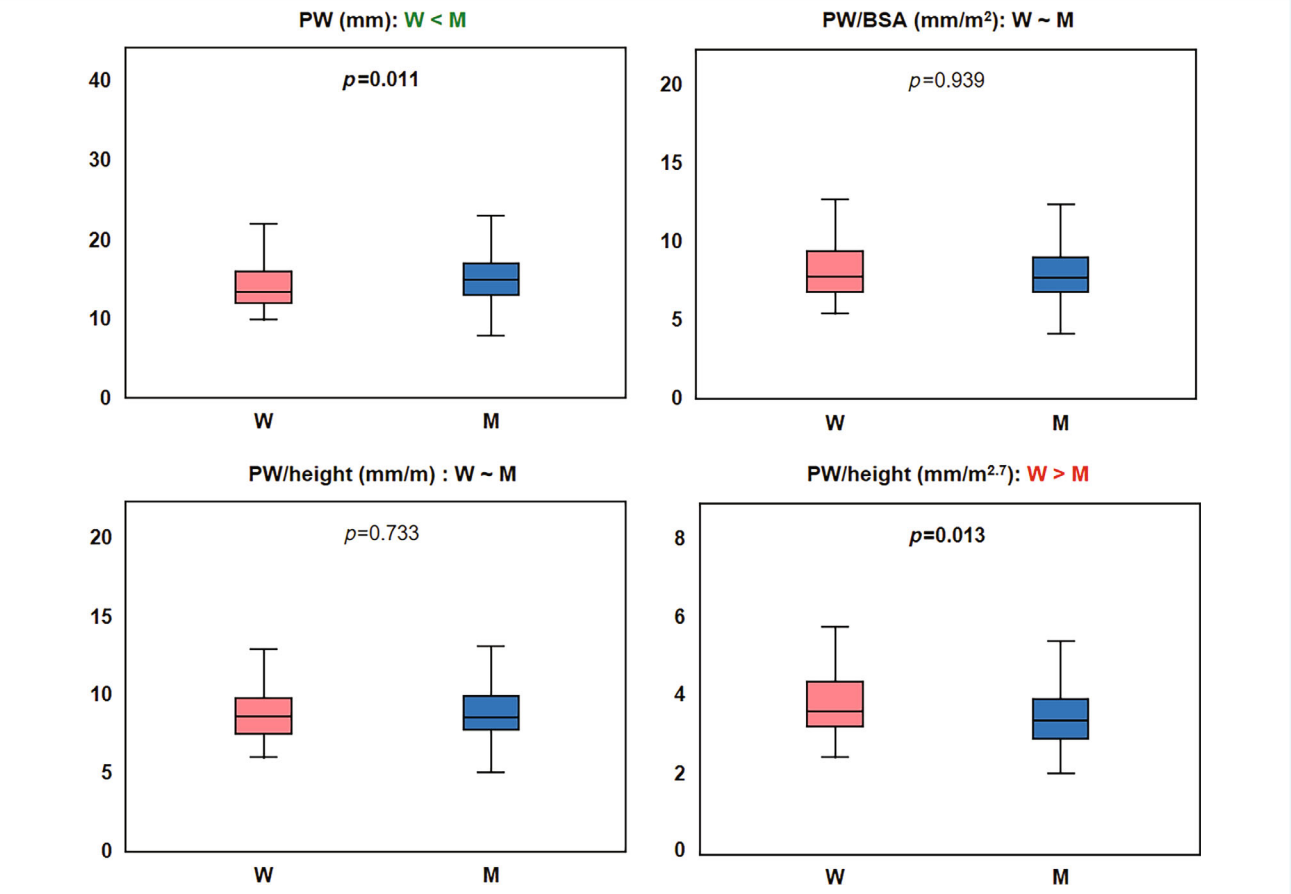

Figure 2 Indexed and not indexed values of posterior wall thickness in women and men. BSA, body surface area; M, men; PW, posterior wall; W, women.

thickness ≥12 mm plus at least one red flag should raise the suspicion of CA.[2] The 12 mm cut-off is not sex-specific, although normal values of LV wall thickness are lower in women: interventricular septum (IVS) thickness, upper reference limit (URL) 11.2 mm in women versus 12.4 mm in men; posterior wall (PW) thickness, URL 11.5 versus 12.3 mm, respectively.[3] Women could then reach the 12 mm threshold when their disease is more advanced, possibly leading to underdiagnosis or delayed diagnosis.

We investigated the relationship between LV wall thickness and the severity of cardiac involvement in women and men with ATTR-CA.

Methods

We evaluated 330 consecutive patients diagnosed with ATTR-CA at three referral centres (Pisa, $n = 232$; Brescia, $n = 69$; Trieste, $n = 29$). We followed the diagnostic workup endorsed by the ESC.[2] Patients were managed according to the recommendations by scientific societies.[4] In January 2023, we retrieved follow-up data from the electronic health records and phone calls to the patients and their relatives. We collected information on all-cause death and heart failure (HF) hospitalization. The study protocol conformed to the 1975 Declaration of Helsinki, and was approved by the Institutional Human Research Committees of each centre. All patients provided written informed consent. Statistical analysis was performed using IBM SPSS Statistics version 23.0 software (SPSS Inc., Chicago, IL, USA). Normal distribution was checked through the Shapiro–Wilk test. All continuous variables were non-normally distributed and were then expressed as median and interquartile range (IQR). Discrete variables were expressed as counts and percentages. Measures of LV wall thickness and mass were indexed for height (in m), height$^{2.7}$, and body surface area (BSA). Comparisons between groups were performed through the Mann–Whitney U test or the Chi-square test, as applicable. The strength of correlations was evaluated through the Spearman correlation coefficient. Patient survival in women and men was compared through Kaplan–Meier curves and the log-rank test, considering a p-value <0.05 as statistically significant. The prognostic value of wall thickness values was investigated also through area under the curve (AUC) values and Cox regression analysis.

Results

The cohort included 330 patients, with 53 women (16%). Most patients had wild-type ATTR-CA. Median age was 4 years higher in women than men ($p = 0.006$). Women had lower height and BSA

Table 2 Correlations between non-indexed and indexed measures of left ventricular wall thickness and cardiac biomarkers

Indexation	NT-proBNP	hs-troponin T	LVEF	GLS*	RWT	E/e'	LAVI	TAPSE	PAPs
IVS									
Non indexed	$p = 0.135$	$p = 0.150$	$p = 0.240$	$p = 0.541$	$p < 0.001$, $r = 0.629$	$p < 0.001$, $r = 0.257$	$p = 0.342$	$p = 0.009$, $r = 0.152$	$p = 0.616$
BSA	$p = 0.026$, $r = 0.141$	$p = 0.105$	$p = 0.156$	$p = 0.193$	$p < 0.001$, $r = 0.650$	$p < 0.001$, $r = 0.254$	$p = 0.104$	$p = 0.001$, $r = 0.207$	$p = 0.032$, $r = 0.130$
Height	$p = 0.029$, $r = 0.139$	$p = 0.100$	$p = 0.218$	$p = 0.347$	$p < 0.001$, $r = 0.682$	$p < 0.001$, $r = 0.282$	$p = 0.189$	$p = 0.001$, $r = 0.196$	$p = 0.186$
Height$^{2.7}$	$p = 0.004$, $r = 0.183$	$p = 0.053$	$p = 0.458$	$p = 0.496$	$p < 0.001$, $r = 0.656$	$p < 0.001$, $r = 0.262$	$p = 0.034$, $r = 0.126$	$p < 0.001$, $r = 0.188$	$p = 0.082$
PW									
Non indexed	$p = 0.431$	$p = 0.724$	$p = 0.591$	$p = 0.838$	$p < 0.001$, $r = 0.370$	$p = 0.034$, $r = 0.123$	$p = 0.093$	$p = 0.007$, $r = 0.155$	$p = 0.962$
BSA	$p = 0.253$	$p = 0.621$	$p = 0.480$	$p = 0.674$	$p < 0.001$, $r = 0.410$	$p = 0.036$, $r = 0.126$	$p = 0.039$, $r = 0.123$	$p = 0.002$, $r = 0.184$	$p = 0.538$
Height	$p = 0.326$	$p = 0.687$	$p = 0.682$	$p = 0.813$	$p < 0.001$, $r = 0.386$	$p = 0.039$, $r = 0.125$	$p = 0.095$	$p = 0.005$, $r = 0.172$	$p = 0.954$
Height$^{2.7}$	$p = 0.145$	$p = 0.528$	$p = 0.759$	$p = 0.774$	$p < 0.001$, $r = 0.411$	$p = 0.029$, $r = 0.132$	$p = 0.030$, $r = 0.129$	$p = 0.003$, $r = 0.177$	$p = 0.538$

BSA, body surface area; hs, high-sensitivity; GLS, global longitudinal strain; IVS, interventricular septum; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAPs, systolic pulmonary artery pressure; PW, posterior wall; RWT, relative wall thickness; TAPSE, tricuspid annular plane systolic excursion.
*Available for 185 patients (56%).

values (both $p < 0.001$). Other clinical and laboratory features did not differ significantly, including N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin T. Conversely, women were more often in National Amyloidosis Centre (NAC) stage 3 (*Table 1*). Fifteen women (28%) and 75 men (27%) died over a median follow-up duration of 2.0 years (IQR 0.9–3.7), with no significant difference in survival free from all-cause death ($p = 0.241$). Similarly, there was no difference in survival free from all-cause death or HF hospitalization (17 vs. 86 events in women vs. men, 1.2 years [0.5–2.1], $p = 0.177$).

Interventricular septum and PW thickness values were lower in women than men, but most differences were abolished when indexing by BSA, height, or height$^{2.7}$, suggesting similar disease severity when accounting for the smaller body size of women. PW thickness indexed for height$^{2.7}$ was even higher in women (*Figures 1* and *2*).

We also searched for correlations between IVS and PW thickness and other indicators of the severity of cardiac disease. IVS values indexed by height$^{2.7}$ displayed tighter associations with NT-proBNP values than non-indexed IVS values. Similarly, indexed values displayed closer relationships with relative wall thickness, E/e' ratio, and tricuspid annular plane systolic excursion (*Table 2*). Both non-indexed and indexed LV thickness values displayed non-significant correlations with LV global longitudinal strain (which was nonetheless available only for 185 patients, 56%).

Both non-indexed and indexed IVS and PW thickness values were poor predictors of outcome, with AUC values ranging between 0.5 and 0.6 and no univariate predictor of outcome (data not shown).

Conclusions

Indexed LV wall thickness values, particularly by height$^{2.7}$, reflect more accurately the severity of cardiac involvement (in terms of NT-proBNP elevation, the degree of concentric remodelling, diastolic dysfunction and right ventricular systolic dysfunction) than non-indexed values. We may then propose to replace the single diagnostic cut-off of 12 mm with LV wall thickness values indexed by height$^{2.7}$. A simpler alternative would be to calculate a cut-off for women based on the mean height of men and women in Europe (1.77 m and 1.65 m, respectively)[5]; given 12 mm the cut-off for men, the corresponding cut-off for women would be 12 mm * (1.65/1.77) = 11 mm.[6] Dedicated studies should investigate the use of indexed LV wall thickness values or sex-specific cut-offs to diagnose ATTR-CA.

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Conflict of interest: none declared.

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