Published in final edited form as:

Am J Cardiol. 2019 July 01; 124(1): 122–130. doi:10.1016/j.amjcard.2019.03.035.

Use of Ventilatory Efficiency Slope as a Marker for Increased Mortality in Wild-Type Transthyretin Cardiac Amyloidosis

Adil Yunis, MD^a, Gheorge Doros, PhD^e, Ivan Luptak, MD, PhD^{a,b,c}, Lawreen H. Connors, PhD^d, and Flora Sam, MD^{a,b,c}

^aWhitaker Cardiovascular Institute; Boston University School of Medicine, Boston Medical Center

^bCardiovascular Section, Boston University School of Medicine, Boston Medical Center

^cEvans Department of Medicine; Boston University School of Medicine, Boston Medical Center

^dAlan and Sandra Gerry Amyloid Research Laboratory in the Amyloidosis Center; Boston University School of Medicine, Boston Medical Center

^eDepartment of Biostatistics, Boston University School of Public Health

Abstract

Wild-type transthyretin amyloidosis (ATTRwt) results in an infiltrative cardiomyopathy often culminating in symptomatic heart failure (HF). The use of cardiopulmonary exercise testing (CPET) in determining outcomes in ATTRwt cardiac amyloidosis is unknown. Given the emergence of novel therapies to treat transthyretin amyloidosis, we sought to investigate the utility of CPET on outcomes in patients with ATTRwt cardiomyopathy. Fifty-six patients, with biopsy and immunohistochemically-proven ATTRwt, were enrolled between 2005–2015, as part of an NIH ATTRwt substudy at the Boston University Amyloidosis Center. Patients were prospectively studied which included laboratory tests, EKG, echocardiography, in addition to CPET. In this cohort of ATTRwt patients that performed CPET were elderly, all were male, and predominantly white (69.9%). The overall median survival was 59.01 months (95% CI 49.29–88.69). By multivariate analysis, CRP [HR 1.10 (1.03–1.18)], decreased sodium [HR 0.75 (0.58–0.97)], creatinine [HR 7.48 (2.44–22.98)] and VE/VCO₂ [HR 1.10 (1.05–1.16)] were significant risk factors for mortality (P<0.05). Peak VO₂ was insignificant by both univariate and multivariate analyses. ATTRwt patients with VE/VCO₂ >40 had a worse median survival of 38.54 months (95% CI 32.63–51.47) vs. 88.69 months (95% CI 56.26–89.49) than patients with VE/VCO₂ slope ≤40. ROC curve showed that the combination of VE/VCO₂, CRP, sodium and creatinine (AUC, 0.89) predicted 1-year mortality in ATTRwt cardiac amyloidosis. In conclusion, increased VE/VCO₂, in combination with CRP, sodium and creatinine, may identify patients at increased

Corresponding Author: Flora Sam, MD., Whitaker Cardiovascular Institute; Cardiovascular Section, Evans Department of Medicine, Boston University School of Medicine, 700 Albany Street, W507, Boston, MA, 02118, Phone: (617) 638-8072; Fax: (617) 638-4066., flora.sam@bmc.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosures
None

risk of death in ATTRwt cardiomyopathy. VE/VCO₂ might have a role in objectively assessing therapeutic response in ATTRwt cardiac amyloidosis.

Keywords

wild-type transthyretin; cardiac amyloidosis; cardiopulmonary exercise testing; VE/VCO₂ slope

Introduction

Wild-type transthyretin (TTR) amyloidosis (ATTRwt), previously referred to as, senile systemic amyloidosis', is characterized by misfolding and deposition of TTR amyloid protein predominantly in the heart, resulting in a progressive infiltrative cardiomyopathy and heart failure (1;2). Nervous system involvement may occur with carpal tunnel syndrome being the most common antecedent finding (3). TTR amyloid deposition, once thought to be an incidental finding, was found in up to 25% of those >85 years in an autopsy study (4). The median survival in ATTRwt cardiac amyloidosis is quite variable and ranges from 2.71 years (5) up to 6.1 years (6). Until recently (7;8) there were limited therapeutic options for ATTR amyloidosis, but promising new drug therapies have emerged demonstrating improvement in survival and 6-minute walk test (8). As such, there is a need to define parameters that may objectively monitor response to therapy and mortality in ATTR. Cardiopulmonary exercise testing (CPET) allows for the assessment of peak oxygen uptake, establishes causes of dyspnea on exertion, is used to assess functional capacity and prognosis for *non-amyloid* heart failure and cardiomyopathies, (9;10) but little is known about its utility in ATTRwt. Unlike a 6-minute walk test (6MWT), there is no learning (11) nor familiarization effect with CPET (12). In the present study, we prospectively evaluated 56 patients with biopsy and immunohistochemically-proven ATTRwt cardiac amyloid who underwent CPET, clinical assessment and non-invasive studies, to identify risk factors of mortality.

Methods

Between 2005–2015, 121 patients with biopsy and immunohistochemically proven ATTRwt were prospectively enrolled in a NIH funded study RO1AG031804 (2) at the Amyloidosis Center at Boston University School of Medicine and Boston Medical Center. Of these, 56 patients with confirmed ATTRwt cardiac amyloidosis completed cardiopulmonary exercise testing (CPET) on initial evaluation and were included in this analysis. The Institutional Review Board approved the study and all subjects gave written informed consent. Clinical and laboratory evaluations, including a medical history, physical examination, electrocardiography, echocardiography (ECG) and CPET testing were performed at this initial visit to the Amyloidosis Center.

ATTRwt amyloidosis was confirmed by biopsy and immunohistochemical staining in all patients. The majority of tissue samples were obtained from endomyocardial biopsy (n=46). ATTRwt amyloidosis was confirmed to a lesser extent in other tissues (fat pad, tenosynovium, small bowel, lung or bladder; n=10). Age, in some cases Tc 99m PYP imaging, absence of a plasma cell dyscrasia and importantly the exclusion of a mutant

transthyretin allele (by genomic DNA sequencing or mass spectrometry) were all used to diagnose ATTRwt.

Patients were classified according to New York Heart Association (NYHA) Functional class I to IV. Clinical course was monitored with regular follow-up at the Amyloidosis Center and if patients were unable to return to the Amyloidosis Center by telephone and/or by contacting referring physicians. The follow-up end-point was all-cause death obtained from medical records or publicly available databases.

Two-dimensional echocardiography was performed using the GE VingMed Vivid FiVe Echocardiography System (GE Vingmed, Milwaukee, WI) with a 2.5-MHz phased-array transducer as described previously (13). Echocardiogram was performed and analyzed in a blinded manner. Left ventricular (LV) ejection fraction (LVEF) was calculated using the modified Simpson's rule. Systolic and diastolic chamber dimensions and wall thickness measurements were obtained by 2D imaging according to the American Society of Echocardiography recommendations (14). The standard cube formula was utilized to calculate left ventricular mass (14). Relative wall thickness (RWT) was calculated as $(2 \times \text{posterior wall thickness}) / \text{left ventricle end-diastolic diameter (LVEDD)}$. The apical 4-chamber view was used to determine transmitral Doppler LV measurements and analyzed for diastolic filling indexes, including peak E- and A-wave velocities, the E/A ratio, and E-wave deceleration time. Myocardial velocity of the mitral annulus and derivation of E' was determined using tissue Doppler imaging. An E' velocity of <10 cm/s by tissue Doppler imaging suggested impaired diastolic function. A higher E/e' index indicated elevated LV end-diastolic pressure (15).

Cardiopulmonary Exercise Testing (CPET) was performed using a standard exercise treadmill with the Medgraphics CPX Ultima. Expired gas analyses were performed, with the highest values obtained during the final 30 seconds of exercise used as peak scores. Peak oxygen consumption ($VO_{2\max}$), ventilatory equivalent for carbon dioxide (VE/VCO_2 slope), tidal volume, exercise duration, breathing reserve and respiratory exchange ratio (RER) were calculated as described (16).

Blood samples were collected at the initial visit to the Amyloidosis Center and included brain natriuretic peptide (BNP), cardiac troponin I, C-reactive protein (CRP), and ESR as part of routine laboratory testing.

Continuous variables were expressed as mean $\pm$ standard deviation and categorical variables were expressed as number of patients and percentages or median (interquartile range). Comparisons between the VE/VCO_2 slope >40 and ≤ 40 groups were evaluated by the Student t test for continuous variables or the chi-square test for categorical variables. However when comparing continuous baseline characteristics here, we report the Wilcoxon's test result whenever the Shapiro-Wilk test for normality is significant ($p < 0.05$). Univariate analyses were performed to identify variables associated with increased mortality from demographic, clinical, laboratory, electrocardiography and echocardiographic variables. A P value ≤ 0.05 was considered statistically significant. Covariates were chosen based on biological and statistical significance and entered into a multivariate Cox

proportional hazards model. Backward elimination was then conducted with *P*-value criteria for retention set at 0.20. As proposed by Heagerty *et al.*(17), to define the predictive accuracy of the Cox regression models under considerations we use the time-dependent accuracy measures (sensitivity, specificity, and ROC concepts). These measures, reported as *t=months*, provide measures to characterize the ability of these markers to distinguish cases from controls. The analyses were conducted using SAS software version 9.4 (SAS Institute Inc.) or R version 3.5.0 (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL<https://www.R-project.org/>).

Results

Of the 121 patients with confirmed ATTRwt cardiac amyloidosis, 56 were able to exercise and underwent CPET, as part of this substudy, on initial enrollment at the Amyloidosis Center (Table 1). All subjects were male, predominantly white and elderly with a mean age of 74.8 ± 6.2 years. The major associated comorbidities were hypertension and atrial fibrillation/atrial flutter. Most patients had heart failure symptoms (>80% were NYHA Functional Class 2). There was evidence of neurologic involvement, the most common of which was carpal tunnel syndrome, that preceded the diagnosis of ATTRwt cardiac amyloidosis. The majority of patients were on loop/thiazide diuretics (88%). Beta-blocker and angiotensin converting enzyme-inhibitor/angiotensin receptor blocker use were present in 66% and 43% of these patients, respectively. Cardiac biomarkers were elevated with a median BNP of 401.5 pg/mL (interquartile range 242.8 – 704.3) and cardiac troponin I of 0.104 ng/mL (interquartile range 0.066 – 0.170). Creatinine, uric acid and ESR levels were also elevated.

QRS duration was prolonged on ECG with evidence of intraventricular conduction delay (52%), right bundle branch block (18%) and left bundle branch block (2%). Echocardiography demonstrated structural cardiac changes as seen in Table 2. Mean LVEF was $50.2 \pm 10.9\%$, with increased interventricular septal thickness (16.2 ± 2.9 mm), posterior wall thickness (15.98 ± 2.7 mm), LV mass (299.3 ± 72.9 g) and RWT (0.74 ± 0.2). Left atrial volume (50.1 ± 13.0 mL/m²) was significantly increased and there was evidence of severe diastolic dysfunction as demonstrated by the increased E/A (2.41 ± 1.20) and E/e' (25.8 ± 11.9) ratios and decreased e' mean (4.41 ± 1.4 cm/s). Pulmonary artery systolic pressures were also elevated (32.8 ± 15.2 mmHg).

Since there are no normal values for CPET in this age group, ATTRwt patients were compared to a group of age-matched control subjects who had no cardiac amyloidosis and no coronary artery disease (CAD); Table 3. These subjects had been referred for atypical chest pain or were interested in participating in an exercise program (n=10). 70% were male and the average age was 75 ± 7.0 years. In the ATTRwt cohort, mean respiratory exchange ratios (RER) was 1.14 ± 0.12 suggesting adequate effort during CPET testing (16), but there was a trend to lower average exercise duration than control subjects (397.93 ± 173.35 vs. 423.00 ± 82.19 ms; *P*=NS). In both groups, 70% of participants achieved ventilatory threshold. Peak VO₂ was reduced in both ATTR and control groups (13.49 ± 4.46 and

13.59±1.26 ml/kg/min, respectively; P=NS), but VE/VCO₂ slope was significantly elevated in ATTRwt as compared to controls (41.3± 9.7 vs. 35.1±3.7; P<0.05 vs. controls).

In the ATTRwt cohort that were able to perform CPET, the overall median survival was 59.01 months (95% CI 49.29 – 88.69). The median follow-up was 35.0 months with a minimum to maximum range of 10.8 – 89.5 months. The 1, 3 and 5 year survival were 96.4% (95% CI 0.86 – 0.99), 76.6% (95% CI 0.61 – 0.87) and 41.3% (95% CI 0.21 – 0.60) respectively. As expected survival was better than the group as a whole where the median survival was 46.69 months (2).

By univariate analyses (Table 4), the strongest risk factor for all-cause mortality were obstructive sleep apnea, diabetes, elevated creatinine, VE/VCO₂, BNP and CRP levels and lower A-velocity, systolic blood pressure, LVEF, and sodium levels (P<0.05). Multivariate analysis (Table 4), using a Cox proportional hazards regression model with backward elimination, was used to evaluate interactions among all the risk factors for overall mortality. Creatinine, VE/VCO₂, CRP and sodium persisted as significant risk factors (P<0.05). The other univariate risk factors entered into the model were not retained by the final multivariate Cox proportional hazards model. Peak VO₂ was not significant for increased death by univariate and multivariable analyses.

To determine the contribution of single variables or the full model as a whole in predicting 1-year mortality, ROC analysis was performed (Figure 1). The AUC values were comparable for CRP (AUC, 0.67), sodium (AUC, 0.63), creatinine (AUC, 0.68) and VE/VCO₂ (AUC, 0.68). However, the inclusive model using all four variables gave the greatest power, AUC of 0.89 in predicting 1-year mortality in ATTRwt cardiac amyloidosis in those who were able to exercise on initial evaluation.

The significant impact of VE/VCO₂ slope on mortality, both by univariate and multivariate analysis, prompted further subgroup analysis of VE/VCO₂ > and < than the median value 40. Baseline demographics and clinical characteristics were compared between the 2 groups (Table 5). ATTRwt patients with VE/VCO₂ slope >40 had lower body mass index (BMI), lower medial e' by tissue Doppler (a measure of early diastolic mitral annular tissue velocity), higher circulating BNP and troponin I levels and lower exercise duration during CPET testing (P<0.05).

Kaplan-Meier survival estimates showed worse survival in VE/VCO₂ slope >40 vs. VE/VCO₂ slope <40 over 8 years (P<0.01; Figure 2). Median survival was significantly worse in those with VE/VCO₂ slope >40 vs. VE/VCO₂ slope <40 [38.54 months (95% CI 32.63–51.47) vs. 88.69 months (95% CI 56.26–89.49); P<0.01]. The 1, 3 and 5-year cumulative survival in VE/VCO₂ slope >40 was 91.7% (95% CI 0.86 – 0.97), 64.1% (95% CI 0.53 – 0.76) and 24.9% (95% CI 0.13 – 0.37) respectively. Conversely, survival was better for those with a VE/VCO₂ slope <40 at those same time-points: 100%, 84.7% (95% CI 0.77 – 0.92) and 56.5% (95% CI 0.39 – 0.73), respectively.

Discussion

In this subgroup study, the increased VE/VCO₂ slope was associated with more severe clinical disease and with increased mortality in ATTRwt cardiac amyloidosis. An inclusive model of increased VE/VCO₂ with elevated CRP, creatinine and low sodium identified those ATTRwt patients at the highest risk of dying at 1 year. Importantly, peak VO₂ was not a risk factor for mortality by univariate or multivariable analysis in this cohort.

Peak VO₂ has long been used in the assessment of functional capacity and as a predictor of survival in heart failure with reduced ejection fraction (HFrEF) (18). This was not seen here and our findings demonstrate the limitations of the prognostic value of peak VO₂ in ATTRwt cardiomyopathy. It had been suggested that patients unable to achieve peak VO₂ might be due to the association of multiple comorbidities, advanced age or performing a submaximal exercise test. (19) The first two are likely relevant to this ATTRwt cohort but 93% of patients in this exercising cohort were able to attain RER (median: 1.13; range: 1.07–1.20).

It is unclear why peak VO₂ does not have a prognostic value in ATTRwt cardiomyopathy. Peak VO₂ is a function of both cardiac output and arterial-venous oxygen difference. During exercise in normal healthy adults, peak VO₂ rises to meet increasing metabolic demand. However, energy expenditure and both its components of active and resting metabolic rate decrease with age (20), leading to age as the strongest predictor of peak VO₂. (21)

Patients with ATTRwt cardiac amyloidosis are thought to phenocopy patients with heart failure with preserved ejection fraction (HFpEF) with clinical heart failure, LV hypertrophy and diastolic dysfunction. (22) VO₂ and VE/VCO₂ slope both have a predictive outcome in HFpEF. (23) However, in a cohort of HFpEF patients where LVEF > 50%, only peak VO₂, and not VE/VCO₂ slope was associated with all-cause mortality or cardiac transplant after adjusting for age, sex, and β -blockade therapy. They were followed for a median of 5.2 years (24) with all patients reaching RER, but the an important difference in addition to being *non-amyloid* HF, was that patients were younger (the mean age was 54±14 years) and 45% were female. Conversely Nadruz et al., showed in *non-amyloid* HF, that both VE/VCO₂ slope in addition to peak VO₂ had greater prognostic discrimination in HFpEF than HFrEF. (23). Other HFpEF studies, similar to our present study, showed that only VE/VCO₂ slope, and not peak VO₂, was associated with all-cause mortality and raised intrapulmonary pressures. (25)

In the present study, VE/VCO₂ persisted as a significant indicator of survival by both univariate and multivariate cox regression analysis in ATTRwt cardiac amyloidosis. Indeed, earlier studies, in patients with *non-amyloid* HF, showed that ventilatory efficiency was an independent prognostic marker. (26;27) As seen in Table 1, most of the ATTRwt patients had heart failure (“diastolic heart failure”) as the mean LVEF was 50.2 ± 10.9%. This was similar to Guazzi et al., who showed in 284 patients with diastolic HF, VE/VCO₂, by multivariate analysis was a significant predictor of mortality. (28)

The mean VE/VCO₂, in this study, was also much higher than the mean value in other studies in patients with *non-amyloid* diastolic HF (27) where those with a higher VE/VCO₂ had a greater mortality. Indeed, the mean VE/VCO₂ was significantly greater in the ATTRwt

cohort as compared to age-matched controls (41.30 ± 9.68 vs. 35.14 ± 3.66 respectively). This might be explained by the augmentation in the ventilatory response leading to elevations in VE/VCO_2 which are linked to reduced pulmonary perfusion, as demonstrated by elevations in pulmonary artery and capillary wedge pressures, as well as ventilation/perfusion mismatch with increased dead space. (19;29) Although hemodynamic measurements were not measured in our study, it is plausible that with the degree of diastolic dysfunction already evident on the baseline, resting echocardiography, these ATTRwt patients likely experienced significant elevations in filling pressures during exercise (as occurs with normal and other HF patients) (30) which resulted in the marked increase in VE/VCO_2 seen in these ATTRwt patients.

Finally those patients with $VE/VCO_2 > 40$ were severely impaired with evidence of poor exercise capacity, elevated cardiac biomarkers and the tissue Doppler measurements of a lower e' medial (demonstrating impaired LV longitudinal myocardial relaxation and diastolic dysfunction).

Until recently, (7;8) there have been limited therapeutic options for ATTR amyloidosis; with limitations associated with organ transplant and traditional guideline-directed heart failure therapies being relatively contraindicated. With the emergence of promising amyloid therapies, the need for reliable non-invasive, objective prognostic markers to assess disease progression and response to therapy is increasingly needed. Further studies are warranted to determine the effectiveness of CRP, creatinine, sodium and VE/VCO_2 in risk stratification and their ability to help guide treatment choices for ATTRwt cardiac amyloidosis.

This prospective cohort study has several limitations. *First*, the Amyloidosis Center at BUMC is a referral center for the diagnosis and treatment of amyloidosis and thus, a referral bias is possible in the selection of patients. *Second*, the predictive model is center-specific and in a small cohort. Like many ATTRwt studies our study sample size was small due to the low disease prevalence and the ability to exercise. Further validation in other cohorts is needed. However, our study participants shared several baseline characteristics and echocardiography parameters with other small cohort studies and is thus likely representative of the greater ATTRwt patient population. *Third*, about 30% of study participants did not attain a ventilatory threshold during CPET. The absence of ventilatory threshold is sometimes cited as reflecting a non-cardiac limitation for exercise and restricts prognostication relative to the underlying cardiomyopathy. However, special consideration must be made for our unique study population. Only a minority of study participants had documented pulmonary or musculoskeletal disease that would prevent the attainment of ventilatory threshold. The absence of ventilatory threshold in some of our study participants is more likely related to their advanced age. It is also possible that ventilatory threshold (16;21) may not be detected in HF patients due to oscillatory ventilation and shorter exercise time. (19;21;29)

Thus in conclusion, CPET testing may be used in ATTRwt cardiac amyloidosis to provide objective measures of prognosis and may assist in assessing outcomes. As such VE/VCO_2 is a useful predictor of mortality. Enhanced prognosis can be made when utilizing VE/VCO_2 slope in a model that includes Cr, sodium and CRP in cardiac amyloidosis.

Acknowledgments

None

Source of Funding

This work was supported by the R. Gordon Darby Research Fund to FS, a grant from the National Institutes of Health (HL117153) to F.S. and (AG031804) to LC.

References

- (1). Falk RH. Diagnosis and Management of the Cardiac Amyloidoses. *Circulation* 2005;112:2047–2060. [PubMed: 16186440]
- (2). Connors LH, Sam F, Skinner M, Salinaro F, Sun F, Ruberg FL, Berk JL, Seldin DC. Heart Failure Resulting From Age-Related Cardiac Amyloid Disease Associated With Wild-Type Transthyretin: A Prospective, Observational Cohort Study. *Circulation* 2016;133:282–290. [PubMed: 26660282]
- (3). Grogan M, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, Klarich KW, Miller WL, Maleszewski JJ, Dispenzieri A. Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System. *J Am Coll Cardiol* 2016;68:1014–1020. [PubMed: 27585505]
- (4). Tanskanen M, Peuralinna T, Polvikoski T, Notkola IL, Sulkava R, Hardy J, Singleton A, Kiuru-Enari S, Paetau A, Tienari PJ, Myllykangas L. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. *Ann Med* 2008;40:232–239. [PubMed: 18382889]
- (5). Pinney JH, Whelan CJ, Petrie A, Dzung J, Banyersad SM, Sattianayagam P, Wechalekar A, Gibbs SD, Venner CP, Wassef N, McCarthy CA, Gilbertson JA, Rowczenio D, Hawkins PN, Gillmore JD, Lachmann HJ. Senile systemic amyloidosis: clinical features at presentation and outcome. *J Am Heart Assoc* 2013;2:e000098. [PubMed: 23608605]
- (6). Gonzalez-Lopez E, Gagliardi C, Dominguez F, Quarta CC, de Haro-Del Moral FJ, Milandri A, Salas C, Cinelli M, Cobo-Marcos M, Lorenzini M, Lara-Pezzi E, Foffi S,onso-Pulpon L, Rapezzi C, Garcia-Pavia P. Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths. *Eur Heart J* 2017;38:1895–1904. [PubMed: 28329248]
- (7). Adams D, Gonzalez-Duarte A, O’Riordan WD, Yang CC, Ueda M, Kristen AV, Tournev I, Schmidt HH, Coelho T, Berk JL, Lin KP, Vita G, Attarian S, Plante-Bordeneuve V, Mezei MM, Campistol JM, Buades J, Brannagan TH III, Kim BJ, Oh J, Parman Y, Sekijima Y, Hawkins PN, Solomon SD, Polydefkis M et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. *N Engl J Med* 2018;379:11–21. [PubMed: 29972753]
- (8). Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *N Engl J Med* 2018;379:1007–1016. [PubMed: 30145929]
- (9). O’Connor CM, Whellan DJ, Wojdyla D, Leifer E, Clare RM, Ellis SJ, Fine LJ, Fleg JL, Zannad F, Keteyian SJ, Kitzman DW, Kraus WE, Rendall D, Pina IL, Cooper LS, Fiuzat M, Lee KL. Factors related to morbidity and mortality in patients with chronic heart failure with systolic dysfunction: the HF-ACTION predictive risk score model. *Circ Heart Fail* 2012;5:63–71. [PubMed: 22114101]
- (10). Gitt AK, Wasserman K, Kilkowski C, Kleemann T, Kilkowski A, Bangert M, Schneider S, Schwarz A, Senges J. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. *Circulation* 2002;106:3079–3084. [PubMed: 12473555]
- (11). Wu G, Sanderson B, Bittner V. The 6-minute walk test: how important is the learning effect? *Am Heart J* 2003;146:129–133. [PubMed: 12851620]

- (12). Bensimhon DR, Leifer ES, Ellis SJ, Fleg JL, Keteyian SJ, Pina IL, Kitzman DW, McKelvie RS, Kraus WE, Forman DE, Kao AJ, Whellan DJ, O'Connor CM, Russell SD. Reproducibility of peak oxygen uptake and other cardiopulmonary exercise testing parameters in patients with heart failure (from the Heart Failure and A Controlled Trial Investigating Outcomes of exercise training). *Am J Cardiol* 2008;102:712–717. [PubMed: 18773994]
- (13). Biolo A, Ramamurthy S, Connors LH, O'Hara CJ, Meier-Ewert HK, Soo Hoo PT, Sawyer DB, Seldin DS, Sam F. Matrix Metalloproteinases and Their Tissue Inhibitors in Cardiac Amyloidosis: Relationship to Structural, Functional Myocardial Changes and to Light Chain Amyloid Deposition. *Circ Heart Fail* 2008;1:249–257. [PubMed: 19808299]
- (14). Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1–39 [PubMed: 25559473]
- (15). Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;29:277–314. [PubMed: 27037982]
- (16). Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Gulati M, Keteyian SJ, Lavie CJ, Macko R, Mancini D, Milani RV. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010;122:191–225. [PubMed: 20585013]
- (17). Heagerty PJ, Zheng Y. Survival Model Predictive Accuracy and ROC Curves. *Biometrics* 2005;61:92–105. [PubMed: 15737082]
- (18). Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr., Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991;83:778–786. [PubMed: 1999029]
- (19). Metra M, Dei CL, Panina G, Visioli O. Exercise hyperventilation chronic congestive heart failure, and its relation to functional capacity and hemodynamics. *Am J Cardiol* 1992;70:622–628. [PubMed: 1510011]
- (20). Manini TM. Energy expenditure and aging. *Ageing Res Rev* 2010;9:1–11. [PubMed: 19698803]
- (21). Forman DE, Clare R, Kitzman DW, Ellis SJ, Fleg JL, Chiara T, Fletcher G, Kraus WE. Relationship of age and exercise performance in patients with heart failure: the HF-ACTION study. *Am Heart J* 2009;158(4 Suppl):S6–S15. [PubMed: 19782790]
- (22). Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, Bornstein B, Salas C, Lara-Pezzi E, Alonso-Pulpon L, Garcia-Pavia P. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J* 2015;36:2585–2594. [PubMed: 26224076]
- (23). Nadruz W Jr., West E, Sengelov M, Santos M, Groarke JD, Forman DE, Claggett B, Skali H, Shah AM. Prognostic Value of Cardiopulmonary Exercise Testing in Heart Failure With Reduced, Midrange, and Preserved Ejection Fraction. *J Am Heart Assoc* 2017;6(11). pii: e006000.
- (24). Shafiq A, Bawner CA, Aldred HA, Lewis B, Williams CT, Tita C, Schairer JR, Ehrman JK, Velez M, Selektor Y, Lanfear DE, Keteyian SJ. Prognostic value of cardiopulmonary exercise testing in heart failure with preserved ejection fraction. The Henry Ford Hospital CardioPulmonary EXercise Testing (FIT-CPX) project. *Am Heart J* 2016;174:167–172. [PubMed: 26995385]
- (25). Klaassen SHC, Liu LCY, Hummel YM, Damman K, van der Meer P, Voors AA, Hoendermis ES, van Veldhuisen DJ. Clinical and Hemodynamic Correlates and Prognostic Value of VE/VCO₂ Slope in Patients With Heart Failure With Preserved Ejection Fraction and Pulmonary Hypertension. *J Card Fail* 2017;23:777–782. [PubMed: 28736291]

- (26). Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Peak VO₂ and VE/VCO₂ slope in patients with heart failure: a prognostic comparison. *Am Heart J* 2004;147:354–360. [PubMed: 14760336]
- (27). Chua TP, Ponikowski P, Harrington D, Anker SD, Webb-Peploe K, Clark AL, Poole-Wilson PA, Coats AJ. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol* 1997;29:1585–1590. [PubMed: 9180123]
- (28). Guazzi M, Myers J, Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. *J Am Coll Cardiol* 2005;46:1883–1890. [PubMed: 16286176]
- (29). Sullivan MJ, Higginbotham MB, Cobb FR. Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities. *Circulation* 1988;77:552–559. [PubMed: 3342486]
- (30). Dorfs S, Zeh W, Hochholzer W, Jander N, Kienzle RP, Pieske B, Neumann FJ. Pulmonary capillary wedge pressure during exercise and long-term mortality in patients with suspected heart failure with preserved ejection fraction. *Eur Heart J* 2014;35:3103–3112. [PubMed: 25161181]

Figure 1:
Receiver-operating characteristic (ROC) curves demonstrated that VE/VCO₂ slope, creatinine, sodium and CRP are predictors of 1-year mortality in patients with ATTRwt cardiac amyloidosis.

Patients, n

$VE/VCO_2 > 40$:	24	22	16	9	5	3	3
$VE/VCO_2 \leq 40$:	31	31	24	16	11	4	2

Figure 2:

Kaplan Meier Survival curve for all-cause mortality in $VE/VCO_2 > 40$ and $VE/VCO_2 \leq 40$ in ATTRwt cardiac amyloidosis. Survival was significantly worse in patients with $VE/VCO_2 > 40$ than those with $VE/VCO_2 \leq 40$ ($P < 0.01$)

Table 1:

Baseline characteristics, in patient with ATTRwt cardiac amyloidosis

Variable	Value (n=56)	Median (IQR range)	Normal values
Age (years)	74.8 ± 6.2	75.5 (71.0 – 79.0)	
Men	56 (100%)		
White	39 (69%)		
Black	2 (4%)		
Hispanic (non-black)	11 (20%)		
Other	4 (7%)		
Body Mass Index (kg/m ²)	28.9 ± 3.9	28.6 (25.3 – 31.2)	
Systolic blood pressure (mmHg)	126.9 ± 16.2	125 (113. – 135.0)	
Diastolic blood pressure (mmHg)	76.3 ± 8.0	74.0 (70.0 – 82.0)	
Pulse rate (bpm)	71.4 ± 11.5	69.0 (63.0 – 78.0)	
Coronary Artery Disease	15 (27%)		
Hypertension	27 (48%)		
Diabetes Mellitus	8 (14%)		
Atrial Fibrillation / Atrial flutter	38 (68%)		
Chronic Kidney Disease	7 (13%)		
Obstructive Sleep Apnea	10 (18%)		
Hypothyroidism	8 (14%)		
NYHA Class	2.27 ± 0.75	2.0 (2.0 – 3.0)	
I	18%		
II	37%		
III	45%		
IV	0		
<i>Electrocardiogram</i>			
QRS duration (ms) on ECG	122.0 ± 32.0	116.0 (94.0 – 150.0)	
LBBB	1 (2%)		
RBBB	10 (18%)		
IVCD	29 (52%)		
First degree AVB	18 (32%)		
<i>Neurologic Involvement</i>			
Peripheral	15 (27%)		
Autonomic	2 (4%)		
Carpal Tunnel	38 (68%)		
<i>Laboratory Data</i>			
BNP (pg/mL)	467.5 ± 308.3	401.5 (242.8 – 704.3)	0 – 176
Troponin I (ng/mL)	0.131 ± 0.097	0.104 (0.066 – 0.170)	< 0.033
ESR (mm/hr)	16.7 ± 12.6	14.0 (7.0 – 23.0)	0 – 20
C-reactive protein (mg/L)	4.2 ± 7.1	1.6 (0.8 – 4.8)	0 – 5.0

Variable	Value (n=56)	Median (IQR range)	Normal values
Hemoglobin (g/dL)	13.4 ± 1.7	13.6 (12.5 – 14.7)	13.5 – 17.5
Sodium (mmol/L)	139.3 ± 2.5	139.0 (138.0 – 141.0)	135 – 145
Creatinine (mg/dL)	1.3 ± 0.4	1.2 (1.0 – 1.5)	0.7 – 1.3
Uric Acid (mg/dL)	7.7 ± 2.1	7.8 (6.0 – 9.1)	2.4 – 6.0
<i>Medications</i>			
Beta blocker	37 (66%)		
ACE-I/ARB	24 (43%)		
Loop/Thiazide Diuretics	49 (88%)		
Aldactone	6 (11%)		
Statin	32 (57%)		
Anticoagulants	36 (64%)		

Data are expressed as mean ± SD for continuous variables or numbers or percent (%) for categorical variables and median (IQR, interquartile range); NYHA, New York Heart

Association; ECG, electrocardiogram; LBBB, left bundle branch block; RBBB, right bundle branch block; IVCD, intraventricular conduction delay; AVB, atrioventricular block; BNP, brain natriuretic peptide; ESR, erythrocyte sedimentation rate; ACE-I, angiotensin converting enzyme-inhibitor; ARB, angiotensin receptor blocker; Anticoagulants include warfarin and non-vitamin K antagonist oral anticoagulants.

Table 2:

Baseline echocardiographic measures at initial clinic visit in ATTRwt cardiac amyloidosis

Variable	Value	Median (IQR range)	Normal Range
<i>LV structure</i>			
Ventricular septum (mm)	16.2 ± 2.9	16 (15 – 18)	< 11
Posterior Wall Thickness (mm)	15.98 ± 2.7	16 (14 – 18)	6 – 11
Relative Wall Thickness	0.74 ± 0.20	0.72 (0.60 – 0.86)	0.22 – 0.42
LV mass index (g/m ²)	149.3 ± 34.5	148.7 (127.7 – 172.2)	< 131 (male)
LV mass (g)	299.3 ± 72.9	294.3 (258 – 340)	67 – 162
<i>LV size</i>			
LV EDD (mm)	45.7 ± 14.9	43 (39 – 49)	< 57
LV ESD (mm)	33.1 ± 6.6	32 (28 – 38)	21 – 40
Left Atria Volume (mL/m ²)	50.3 ± 13.0	49.3 (41.3 – 56.0)	34
Left Atria (mm)	42.6 ± 4.9	43 (40 – 46.0)	
<i>LV function</i>			
LV EF (%)	50.2 ± 10.9	50 (40 – 60)	> 50
E/A	2.41 ± 1.20	2.35 (1.5 – 3.2)	0.9 [†]
e' medial (cm/s)	3.69 ± 1.3	3.4 (3.0 – 4.6)	~7.5 [†]
e' lateral (cm/s)	5.14 ± 1.8	5.0 (4.0 – 6.0)	~10.5 [†]
e' mean (cm/s)	4.41 ± 1.4	4 (3.5 – 5.5)	~9.0 [†]
E/e'	25.8 ± 11.9	21.5 (17 – 29)	< 8
PA systolic pressure (mmHg)	32.8 ± 15.2	36.5 (29 – 42)	15 – 25

Data are expressed as mean ± SD for continuous variables and mean (IQR, interquartile range). LV indicates left ventricular; EDD, end-diastolic diameter; ESD, end-systolic diameter; EF, ejection fraction; PA, pulmonary artery. E/A, mitral inflow E/A ratio; e', early diastolic velocity; E/e', ratio between early mitral inflow velocity and mitral annular early diastolic velocity.

[†]Age-specific normal reference ranges for age 65–75 years (Chahal NS, Lim TK, Jain P, Chambers JC, Kooner JS, Senior R. Normative reference values for the tissue Doppler imaging parameters of left ventricular function: a population-based study. Eur J Echocardiogr 2010;11:51–6).

Other normal values per American Society of Echocardiography (14)

Table 3:

Cardiopulmonary exercise testing (CPET) in ATTRwt cardiac amyloidosis compared to age and sex-matched controls

CPET Variables	ATTRwt	Controls
Peak VO ₂ (mL kg min)	13.49 ± 4.46 *13.35 (9.63 – 16.33)	13.59 ± 1.26
VE/VCO ₂ Slope	41.30 ± 9.68 *40 (34 – 46)	35.14 ± 3.66
1 - Ventilatory Reserve (VE/MVV) (%)	42.79 ± 16.18 *43.5 (32.75 – 55.0)	70.28 ± 4.27
RER	1.14 ± 0.12 *1.13 (1.07 – 1.2)	1.06 ± 0.02
Exercise Duration (s)	397.93 ± 173.35 *360 (300 – 540)	433.00 ± 82.19
VT (mLkgmin)	11.94 ± 4.45 *10.90 (8.8 – 15)	12.90 ± 0.93

Data are expressed as mean ± SD for continuous variables and *median (IQR, interquartile range). Controls (70 % male; age 75± 7 years; n=10). VO₂, Oxygen uptake; VE/VCO₂, ventilatory equivalent for carbon dioxide; RER, respiratory exchange ratio; VE, minute ventilation; MVV, maximum voluntary ventilation; VT, ventilatory threshold.

Table 4:

Univariate and multivariate analysis for predictors of mortality in ATTRwt cardiac amyloidosis who performed CPET

Variable	Univariate Hazard Ratio	P-Value	Multivariate Hazard Ratio	P-Value
Obstructive sleep apnea	3.81 (1.41 – 10.26)	0.0082		
Diabetes	3.20 (1.12 – 9.13)	0.0293		
BNP	1.00 (1.001 – 1.003)	0.0012		
A-velocity	0.95 (0.91 – 0.99)	0.0284		
Systolic blood pressure	0.95 (0.92 – 0.99)	0.0137		
LVEF (%)	0.95 (0.91 – 0.99)	0.0235		
<i>peak VO₂</i>	<i>0.91 (0.83 – 1.01)</i>	<i>0.0662[†]</i>		
Creatinine	4.18 (1.68 – 10.42)	0.0021	7.48 (2.44 – 22.98)	0.0004
VE/VCO ₂ slope	1.06 (1.02 – 1.10)	0.0012	1.10 (1.05 – 1.16)	0.0003
C-reactive protein	1.07 (1.02 – 1.12)	0.0073	1.10 (1.03 – 1.18)	0.0031
Sodium	0.84 (0.71 – 0.99)	0.0350	0.75 (0.58 – 0.97)	0.0291

BNP, brain natriuretic peptide; A-velocity, reflects the LA-LV pressure gradient during late diastole; LVEF, left ventricular ejection fraction; peak VO₂, peak oxygen uptake; VE/VCO₂, minute ventilation/carbon dioxide production.

[†]P=NS.

Table 5:Clinical Characteristics above and below the median for VE/VCO₂ slope

Variables	VE/VCO2 slope >40 (N=24)	VE/VCO2 slope ≤40 (N=31)	P-value
Age (years)	76.4 ± 3.9	73.6 ± 7.4	0.254
	* 76 (73.5 – 79.5)	* 75 (67 – 79)	
White	13 (54%)	26 (84%)	0.016*
Systolic blood pressure (mmHg)	123.5 ± 18	130 ± 14.5	0.144
	* 123 (110 – 127)	* 131 (120 – 139)	
Body mass index (kg/m ²)	27.8 ± 3.7	29.9 ± 3.9	0.049
	* 27.5 (24.9 – 29.9)	* 29.2 (27.2 – 33.1)	
Hypertension	13 (54%)	14 (45%)	0.508
Diabetes mellitus	5 (21%)	3 (10%)	0.244
Coronary artery disease	5 (21%)	9 (29%)	0.488
Carpal tunnel	15 (63%)	23 (74%)	0.352
NYHA class	2.4 ± 0.7	2.2 ± 0.8	0.270
	*2.5 (2 – 3)	* 2.0 (1 – 3)	
Echocardiography			
LVEF (%)	49.2 ± 11.8	50.5 ± 10.2	0.714
	* 49.5 (42.5 – 60)	* 50 (40 – 60)	
LV mass index (g/m ²)	149.6 ± 34.6	150.1 ± 35.3	0.962
	* 153.3 (124 – 173.5)	* 147.1 (132.5 – 170)	
RWT	0.79 ± 0.23	0.69 ± 0.16	0.062
	* 0.82 (0.66 – 0.93)	* 0.69 (0.58 – 0.76)	
E/A	2.63 ± 1.28	2.24 ± 1.2	0.327
	* 2.49 (1.63 – 3.63)	* 2.12 (1.22 – 3)	
Tissue Doppler e' medial (cm/s)	3.28 ± 1.01	3.99 ± 1.39	0.044*
	* 3 (2.7 – 4)	* 3.8 (3 – 5)	
E/e'	26.85 ± 11.97	25.06 ± 12.28	0.607
	*24 (17.6 – 30)	* 20 (16.4 – 29)	
PA systolic pressure (mmHg)	34 ± 16.1	31.4 ± 14.8	0.506
	* 36 (30 – 46)	* 36 (27 – 41.5)	
Laboratory data			
BNP (pg/mL)	600.2 ± 325.9	375.0 ± 257.9	0.009*
	* 448 (364 – 777)	* 295 (188 – 469)	
Troponin I (ng/mL)	0.17 ± 0.11	0.1 ± 0.08	0.002*
	*0.16 (0.12 – 0.2)	*0.08 (0.05 – 0.12)	
C-reactive protein (mg/L)	3.68 ± 4.11	4.69 ± 8.62	0.918
	* 3.1 (0.8 – 4.5)	* 1.45 (0.8 – 5.2)	
Sodium (mmol/L)	139.1 ± 2.95	139.6 ± 2.06	0.904
	* 139 (138 – 141)	* 140 (138 – 141)	

Variables	VE/VCO ₂ slope >40 (N=24)	VE/VCO ₂ slope 40 (N=31)	P-value
	1.44 ± 0.48	1.25 ± 0.34	
Creatinine	* 1.37 (1.08 – 1.6)	* 1.17 (0.98 – 1.42)	0.116
	7.8 ± 2.1	7.7 ± 2.1	
Uric acid (mg/dl)	* 8.25 (6.35 – 9.3)	* 7.7 (6 – 9.1)	0.824
Exercise testing (CPET)			
	12.2 ± 4.4	14.4 ± 4.4	
Peak VO ₂ (mL kg min)	* 10.85 (8.75 – 14.8)	* 14.8 (10.3 – 17)	0.048
	328.2 ± 149.6	445.1 ± 176.0	
Exercise Duration (s)	* 335 (237 – 420)	* 420 (300 – 592)	0.013*
	10.39 ± 5.1	12.94 ± 3.78	
VT (mLkgmin)	* 9.25 (7.6 – 12.3)	* 12.85 (9.8 – 16.2)	0.083
1 - Ventilatory Reserve (VE/MVV) (%)	0.41 ± 0.18	0.43 ± 0.15	
	* 0.42 (0.32 – 0.55)	* 0.44 (0.34 – 0.56)	0.765
	1.12 ± 0.08	1.16 ± 0.14	
RER	* 1.13 (1.08 – 1.16)	* 1.13 (1.04 – 1.25)	0.615

Data are expressed as mean ± SD or median (range) for continuous variables or numbers (%) for categorical variables and * median (IQR, interquartile range). NYHA, New York Heart Association; BNP, brain natriuretic peptide; LV, left ventricular; EF, ejection fraction; RWT, relative wall thickness; PA, pulmonary artery. E/A, mitral inflow E/A ratio; e', early diastolic velocity; E/e', ratio between early mitral inflow velocity and mitral annular early diastolic velocity; VO₂, Oxygen uptake; VE/VCO₂, ventilatory equivalent for carbon dioxide; RER, respiratory exchange ratio; VE, minute ventilation; MVV, maximum voluntary ventilation; VT, ventilatory threshold.