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EDITORIAL

Untangling the physiology of transthyretin cardiac amyloidosis by leveraging echocardiographically derived pressure–volume indices

Hannah Rosenblum[1], Daniel Burkhoff [2], and Mathew S. Maurer[1]*

[1]Center for Cardiac Amyloidosis, Division of Cardiology, Columbia University College of Physicians & Surgeons, New York, NY, USA; and [2]Cardiovascular Research Foundation, New York, NY, USA

This editorial refers to 'Echocardiographic phenotype and prognosis in transthyretin cardiac amyloidosis', by L. Chacko *et al.*, doi:10.1093/eurheartj/ehz905.

Transthyretin cardiac amyloidosis (ATTR-CA) is the most common aetiology of restrictive cardiomyopathy in older adults and is increasingly being recognized by providers due the advent of non-invasive diagnostic methods[1] and the development of effective therapies that reduce morbidity and mortality.[2] Depending on the presence or absence of mutations, ATTR-CA is classified as either wild-type (wtATTR) or variant (ATTRv) amyloidosis. Patients with wtATTR have a more indolent course, whereas those with ATTRv, especially those with the Val122Ile variant, have more rapid progression marked by significantly worse survival.[3] In this issue of the *European Heart Journal*, Chacko *et al.* confirm these findings in a large population-based cohort study of 1240 patients with ATTR-CA referred over a decade to the National Amyloidosis Centre (NAC), including 474 patients with ATTRv of whom 314 have the Val122Ile variant and 127 the Thr60Ala variant, and 766 patients with wtATTR.[4] At median follow-up of 32 months, 39% of patients died, including 50% with Val122Ile, 43% with Thr60Ala, and 37% with wtATTR. Accordingly, median survival was worse for those with the Val122Ile variant (36 months) and better in those with the Thr60Ala variant (>60 months), compared with wtATTR (58 months). Notably, patients with severe aortic stenosis and ATTR-CA (n = 22, 1.8%) had significantly worse survival. While recent findings demonstrate a prevalence of ATTR-CA in 8–16% of patients with severe aortic stenosis undergoing surgical or percutaneous aortic valve replacement,[5] these data demonstrate that the majority of patients with ATTR-CA do not have co-existing severe aortic stenosis.

This study comprehensively investigates echocardiographic phenotypes of both wtATTR and ATTRv and identifies parameters predictive of survival. Despite similar wall thickness at diagnosis, patients with the Val122Ile variant have echocardiographic features indicative of more advanced disease at diagnosis, with compromised systolic and diastolic left ventricular function and evidence of impaired right ventricular function, whereas those with Thr60Ala have echocardiographic characteristics suggestive of a milder phenotype. In multivariable Cox proportional hazard models, even after accounting for biomarker staging[6] and New York Heart Association class,[7] two of the most robust factors associated with prognosis, both longitudinal strain and stroke volume index, emerge as significant predictors of mortality.

Global longitudinal strain has been previously demonstrated in both light chain amyloidosis and ATTR-CA to be independently associated with outcomes.[8,9] While it is increasingly being utilized in echocardiographic laboratories and there is a strong case to be made for routine measurement especially in amyloid heart disease,[10] widespread application has been limited by technical limitations resulting from suboptimal image acquisition, concerns regarding differing results across proprietary platforms that could hinder longitudinal interpretations, and the physiological relevance of such measures to well-established organ-level physiological indices. Indeed modelling experiments suggest that myocardial strains are sensitive to not only left ventricular contractility, but also to the left ventricular loading conditions, especially to changes in afterload.[11]

Stroke volume, however, has been quantified for decades on echocardiography derived either by left ventricular volumes, as done in the current study,[4] or by Doppler estimates of aortic outflow. In the current study, the stroke volume index emerged as an important simple measure that is prognostic, as has been shown in AL cardiac amyloidosis.[12] To gain important insights into why stroke volume is prognostic in this setting, non-invasive ventricular pressure–volume

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* Corresponding author. Columbia University Medical Center, Clinical Cardiovascular Research Laboratory for the Elderly, Allen Hospital of New York Presbyterian, 5141 Broadway, 3 Field West Room 035, New York, NY 10034, USA. Tel: +1 212 932 4537, Fax: +1 212 932 4538, Email: Msm10@cumc.columbia.edu

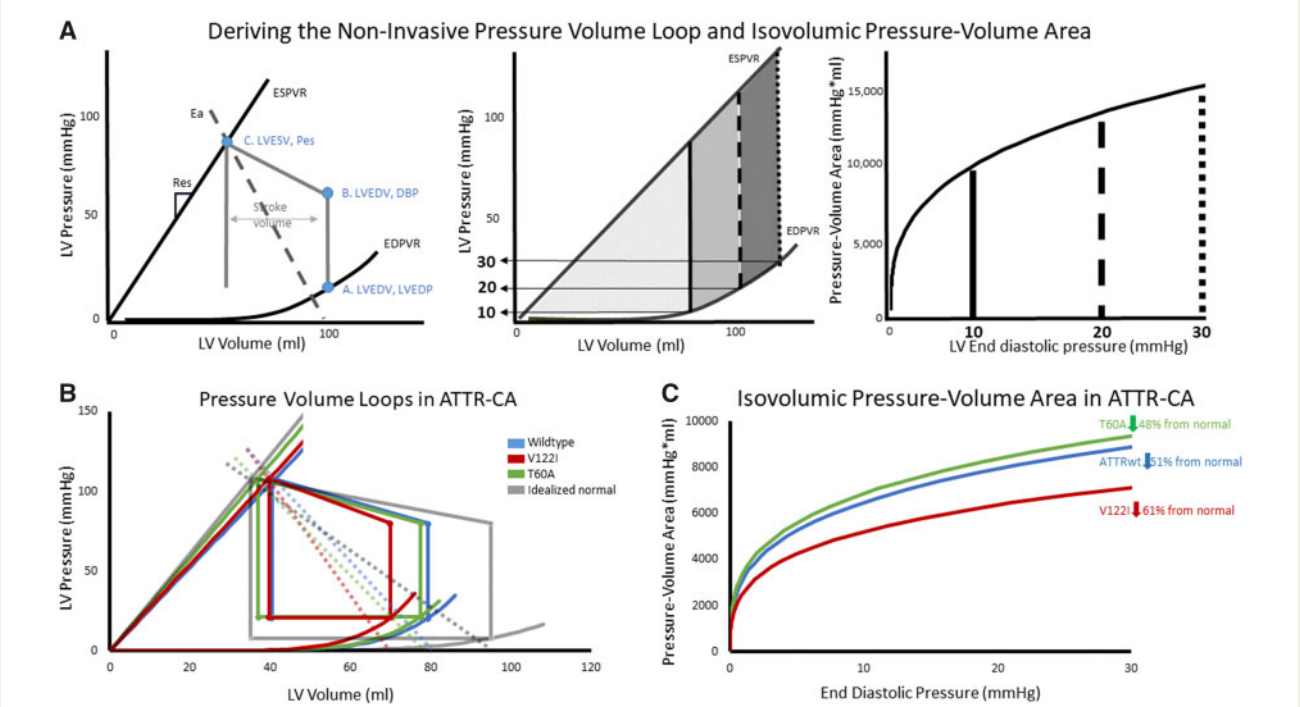

Figure 1 Non-invasive estimates of pressure–volume relationships in ATTR-CA. (*A*) Methods to estimate pressure–volume relationships and derive the isovolumic pressure–volume area. Left: the pressure–volume loop is constructed from three pressure points on the pressure–volume plane, estimated from brachial systolic (SBP) and diastolic blood pressure (DBP), left ventricular end-diastolic (LVEDV) and end-systolic volume (LVESV), and Doppler-based estimates of left ventricular end-diastolic pressure (LVEDP). The end-systolic pressure (Pes) is estimated at 0.9 × SBP. The end-diastolic pressure is estimated by 11.96 + 0.596 × (E/e').[14] Cardiac chamber contractility is represented by the end-systolic pressure–volume relationship (ESPVR) in this case estimated by the ratio of end-systolic pressure to end-systolic volume (Res) in which V_0 is assumed to be 0 mL. Passive properties of the ventricle are represented by the end-diastolic pressure–volume relationship (EDPVR) derived from single beat methods.[14] Arterial elastance (Ea) is a measure of the hydraulic load of the arterial system imposed on the ventricle and is measured by Pes divided by stroke volume. Middle: the area between the ESPVR and the EDPVR, the isovolumic pressure–volume area (PVA_{iso}), represents a metric of chamber function independent of afterload, which can be indexed to LV filling (LVEDP) to obtain the EDP–PVA_{iso} relationship. The area to the left of the solid, dashed, and dotted lines correspond to PVA_{iso} at end-diastolic pressures of 10, 20, and 30 mmHg. respectively. Right: the PVA_{iso} measured at LVEDPs of 10, 20, and 30 mmHg, respectively. (B) Representative group average pressure–volume curves,[4,5] showing upward shift in the EDPVR and downward shifts in ESPVR in ATTR-CA (blue, wild type; red, V122I; green, T60A) compared with idealized normal pressure–volume curves (grey). (*C*) Severe decrements in the EDP–PVA_{iso} relationship in ATTR-CA (blue, wild type; red, V122I; green, T60A) with the lowest chamber function in Val122Ile variant subjects.

analysis can be applied by including information about blood pressure.[6] The pressure–volume loop is determined by the systolic and diastolic chamber properties, as well as ventricular preload and arterial afterload resistance, and is the most thorough means of characterizing cardiac chamber properties and understanding ventricular–vascular coupling. While traditionally measured using invasive conductance catheter methods, pressure–volume analysis can be accurately estimated by non-invasive techniques (*Figure 1A*).[13,14]

Non-invasively estimated pressure–volume analysis from the Transthyretin Amyloid Cardiac Study (TRACS) cohort study noted significant differences in pressure–volume relationships between patients with wtATTR and ATTRv with the Val122Ile variant. Those with the Val122Ile variant had significantly impaired systolic and diastolic function, marked by downward shifting of the end-systolic pressure–volume relationship (ESPVR) and upward shifting of the end-diastolic pressure–volume relationship (EDPVR). Furthermore, ventricular–vascular mismatch as evidenced by impaired contractility with concurrent increased effective arterial elastance (Ea) was more prominent in those with the Val122Ile variant. Overall, ventricular pump function indexed by the relationship between left ventricular end-diastolic pressure (EDP) and the isovolumic pressure–volume area (PVA_{iso}) was significantly impaired in those with the Val122Ile variant compared with those with wtATTR. These derangements in the EDP–PVA_{iso} relationship were identifiable prior to significant reductions in ejection fraction and correlated with survival outcomes.[15] However, TRACS was a small cohort of patients with the potential for significant selection bias.

Leveraging the current large, representative data collected by the NAC in London published in this issue,[4] we performed idealized group-averaged pressure–volume analysis from the measured echocardiographic data and previously described blood pressures from the same centre[6] (*Figure 1B*) to delineate the complex changes in

cardiovascular mechanics associated with different disease phenotypes. The data from which these are derived are unique in that they are population based, as all patients with amyloidosis in the UK are seen in the NAC, and they include sophisticated state-of-the-art echocardiographic measures. Compared with idealized normal pressure–volume loops, all patients with ATTR-CA demonstrate impaired diastolic properties with leftward shifted EDPVR, most prominently observed in those with the Val122Ile variant. The ESPVR was relatively preserved across subgroups compared with idealized normal values and, accordingly, the greatest reduction in stroke volume and stroke work is observed in those with the Val122Ile variant. The estimated EDP–PVA_{iso} relationship (*Figure 1C*) is most compromised in those with Val122Ile and less so in those with Thr60Ala and ATTRwt, although all subtypes of ATTR-CA dramatically deviate from idealized normal conditions. Furthermore, ventricular–vascular mismatch as indexed by a markedly increased Ea/Res ratio is most notable in those with Val122Ile compared with those with Thr60Ala or wtATTR. Collectively, these findings illustrate significant decrements in cardiac chamber pump function that are less evident than seen with traditional echocardiographic measures, especially left ventricular ejection fraction, and seem to correlate with the reported outcomes. Untangling these complex haemodynamic interactions could provide a deeper understanding of why the simple metric of stroke volume index emerges as a predictor of death in ATTR-CA.

The estimated pressure–volume relationships represent group-averaged data and therefore we cannot comment on individual deviations from these grouped values. There are likely to be patients within each group that do not follow these patterns. However, these data do suggest that pressure–volume analysis may be used to further our understanding of disease phenotypes in ATTR-CA and can be used to more fully evaluate changes in cardiac mechanics with emerging therapeutics using patient level data.

Chacko and colleagues present important findings regarding prognostication of ATTR-CA using echocardiographic parameters, enabling further understanding of risk stratification in ATTR-CA. Importantly, stroke volume index and global longitudinal strain emerge in multivariable models as predictors of death with a c-statistic of 0.69, suggesting modest prediction. Thus, while echocardiographic parameters are associated with survival in ATTR-CA and seem to offer prognostic information, whether these can be improved on with indexes derived from non-invasive pressure–volume analysis awaits further study. Based upon theoretical considerations, serial pressure–volume analysis allows for load-independent quantification of changes in pump function using the EDP–PVA_{iso} relationship, and for quantifying the underlying contributions of changes in diastolic properties (EDPVR), systolic properties (ESPVR), and vascular properties (Ea). Thus, in general, indices derived from ventricular pressure–volume analysis are ideally suited to provide mechanistic insights and prognostic information well beyond those of standard echocardiographic parameters. The hope is that such measures could be used to provide further mechanistic insight into how ATTR-CA progresses, responds to emerging treatments, and affects chambers other than the left ventricle.

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