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Left Ventricular Myocardial Work to Differentiate Cardiac Amyloidosis From Hypertrophic Cardiomyopathy

Cardiac amyloidosis (CA) is a progressive disorder with a reported median survival of 2.5 to 3.5 years after diagnosis.[1] Novel treatment options are emerging that could improve prognosis but seem most efficient when started at an early stage of the disease, underscoring the importance of early diagnosis. Echocardiography is the first-line imaging technique for the assessment of cardiac structure and function and might raise suspicion of CA. Although "relative apical sparing" of speckle-tracking-derived left ventricular (LV) longitudinal strain (LS) measurements was suggested to help diagnose CA,[2] differentiating CA from other causes of LV hypertrophy remains difficult. Assessment of LV myocardial work (MW) is a novel, noninvasive method to characterize LV systolic function, taking into consideration LV afterload. The aim of the current study was to assess the added value of LV MW measurements (and in particular of constructive work [CW]), to distinguish CA from hypertrophic cardiomyopathy (HCM), when evaluating patients presenting with LV hypertrophy.

Eighty-three CA and 83 HCM (excluding apical HCM) patients, diagnosed between 2003 and 2019 and matched for age (59 ± 12 years) and septal thickness (17 ± 3 mm), were included. Disease diagnosis was made according to current guidelines.[3,4] The study was approved by the institutional review boards. Left ventricular LS was measured using automated function imaging (EchoPAC, ver. 202, GE Medical Systems, Horten, Norway). The LV MW calculation has been described elsewhere.[5] Briefly, LV LS measurements and noninvasive brachial blood pressure measures were combined, and the software created a noninvasive LV pressure-strain curve for the entire cardiac cycle. Left ventricular CW was defined as the work that results by shortening during systole and lengthening during isovolumic relaxation. Left ventricular global LS and LV global CW were averaged from 17 LV segments. Relative apical LS was calculated as average apical LS/(average basal LS + average mid LS). A relative apical LS value ≥ 1 ("apical sparing") has previously been proposed for diagnosing CA.[2] *Relative* apical CW was not calculated, because this ratio does not adjust for LV afterload (having the blood pressure in both the numerator and denominator) and is therefore not different from relative apical LS. Receiver operating characteristics curves and binary regression analysis were performed, using CA as the outcome variable, to investigate whether relative apical LS and LV global LS or LV global

Drs. Stassen and Tjahjadi contributed equally to this work.

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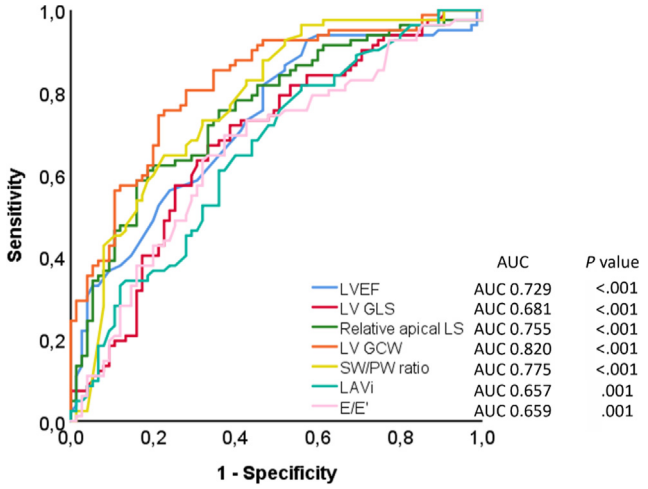

Figure 1 Comparison of receiver operating characteristic curves of LV global CW and other measurements of LV systolic and diastolic function. *GCW*, Global contractile work; *GLS*, global LS; *LAVi*, left atrial volume index; *LVEF*, ejection fraction; *PW*, posterior wall; *SW*, septal wall.

CW had an independent diagnostic value for detection of CA, in addition to standard echocardiographic measures.

Symptoms (defined as New York Heart Association class III-IV) were more prevalent in CA than in HCM patients (33% vs 4%, $P < .001$), although diuretic use was not different between groups (25% vs 29%, $P = .600$). Prevalence of LV hypertrophy on electrocardiogram was higher in patients with HCM (22% vs 5%, $P < .001$). Left ventricular diastolic dysfunction was more pronounced in CA patients, with larger left atrial volume index (45 ± 16 vs 36 ± 14 mL/m^2, $P < .001$), higher E/e' (17 [12-24] vs 12 [9-18], $P < .001$), and higher pulmonary artery pressures (38 ± 14 vs 27 ± 9 mm Hg, $P < .001$). In addition, septal to posterior wall thickness ratio was higher in HCM than in CA patients (1.4 vs 1.2, $P < .001$). Left ventricular systolic function parameters, assessed with LV ejection fraction (53% ± 13% vs 63% ± 13%), LV global LS (12% ± 5% vs 14% ± 5%), and LV global CW (1,022 ± 542 vs 1,793 ± 603 mm Hg%) were all significantly more impaired in CA patients ($P < .001$ for all). Relative apical LV LS ≥ 1 was able to detect CA in only 31/83 (37%) cases but had a larger area under the curve (AUC; 0.755) than LV global LS (AUC = 0.681). However, when looking at LV function global measurements, LV global CW (AUC = 0.820) discriminated CA from HCM better than LV global LS (AUC = 0.681), relative apical LV LS (AUC = 0.755), LV ejection fraction (0.729), septal to posterior wall thickness ratio (AUC = 0.775), left atrial volume index (AUC = 0.657), or E/e' (AUC = 0.659; Figure 1). Receiver operating characteristics analysis showed an optimal LV global CW cutoff value of 1,541 mm Hg% to differentiate CA from HCM (sensitivity = 86%, specificity = 70%). Left ventricular global CW < 1,541 mm Hg% was able to detect CA in 43/52 (83%) patients having a relative apical LV LS < 1. On binary logistic regression analysis (adjusting for LV hypertrophy on electrocardiogram, New York Heart Association functional class III-IV, left atrial volume index, and E/e'), relative apical LV LS ($\beta = 4.760$; 95% CI, 1.306-17.356, $P = .018$) was independently associated with the diagnosis of CA. Importantly, whereas LV global CW ($\beta = 0.998$; 95% CI, 0.997-0.999; $P < .001$) was independently associated with the diagnosis of CA, LV global LS ($\beta = 1.115$; 95% CI, 0.987-1.260; $P = .081$) was not. These findings suggest the importance of adjusting the measures of LV systolic function for afterload in patients with CA, who often present with low blood pressure and possibly therefore an overestimation of LV systolic function according to other measures such as LV ejection fraction and LV LS. In addition, the combination of global and regional MW measurements may better reflect the complex alterations occurring at the myocardial level in CA and therefore have additional value to identify CA patients. Particularly, in patients with a relative apical LV LS (or relative apical LV CW) < 1, lower values of LV global CW should still raise the suspicion of CA and prompt the physician to further investigate the presence of CA.

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Relative Apical Sparing of Longitudinal Strain in Cardiac Amyloidosis: An Intervendor Software Variability Assessment

The relative sparing of regional longitudinal strain (LS) in the apex compared to the mid and basal left ventricular (LV) regions is a valuable clue in the echocardiographic detection of cardiac amyloidosis (CA).[1] Phelan *et al.*[2] found that a relative apical strain ratio (RASR) threshold of 2, defined as the mean apical LS being twice the mean strain in the remainder of the heart using EchoPAC postprocessing software (General Electric Medical Systems), was highly sensitive and specific for the diagnosis of CA. However, segmental and regional LS measurement has continued to demonstrate high variability across different software vendors.[3,4] A recent study of 18 patients with CA demonstrated differences in regional LS values across 3 vendors, impacting intervendor diagnostic accuracy for CA.[5] We sought to add to this emerging evidence by (1) assessing the intervendor variation in regional LS values and RASR in a larger cohort of CA patients and (2) evaluating the diagnostic performance of a previously validated RASR threshold using 2 major software vendors.

The study was approved by the Northwestern University Institutional Review Board. This was a retrospective study of 48 patients with a confirmed diagnosis of CA and an echocardiogram available for review. The medical record for each patient was reviewed to confirm the diagnosis of CA and to ensure their echocardiograms had adequate views. The control group consisted of 52 patients with thickened LVs of varying non-CA etiologies. We excluded patients with atrial fibrillation observed during the echocardiogram due to difficulty measuring strain with beat-to-beat variability. Speckle-tracking strain imaging was performed, and segmental LV LS was analyzed for each patient using 2 dedicated software packages: EchoPAC (ver. 202.0.0. Advanced Analysis Technologies, GE Medical Systems) and TomTEC Imaging Arena (ver. TTA2.42.00, TOMTEC Imaging Systems; Supplemental Figure 1). The RASR for each software system was then calculated as

$$\textit{Relative apical strain ratio (RASR)} = \frac{\textit{Average apical LS}}{\textit{Average (basal LSmid LS)}}$$

Note that this differs in an important respect from the formula used in the original Phelan *et al.*[2] article, which used the sum of the basal and mid LS and so produces values exactly half of those of the new RASR formula. Thus, the diagnostic cutoff of 1 found in Phelan *et al.* would correspond to a value of 2 with our formulation. We felt this change in definition was more intuitive: the apical strain is twice the rest of the heart.

We used Student *t* test and Bland-Altman analysis to assess intervendor agreement of regional LS and RASR. We performed receiver operating characteristic curve analysis to assess each vendor's performance in diagnosing CA. We additionally performed a blinded, qualitative subgroup analysis (random selection of 10 CA and 10 LV hypertrophy [LVH] patients) comparing visual presence of the apical sparing pattern on bull's-eye plots by vendor.

Baseline demographic and echocardiographic data for patients are shown in Table 1. Among the 48 patients with CA, 19 had transthyretin CA and 29 had amyloid light chain CA; among the nonamyloid LVH cohort, 13 patients had hypertensive LVH, 22 had hypertrophic cardiomyopathy, and 17 had moderate-severe aortic stenosis. The overall CA cohort displayed lower LV ejection fraction, a more dilated LV, and evidence of more advanced diastolic dysfunction than patients in the comparator group. Bland-Altman and Student *t* test results are shown in Table 2. Differences in regional LS between vendors were most pronounced at the LV apex, where there was a statistically and clinically significant difference in mean LS (−16.8% vs −13.5% for EchoPAC and TomTEC, respectively). Bland-Altman agreement testing revealed a significant mean bias of 3.24% for mean apical LS with limits of agreement of 11.3% ($P < .001$), which was associated with a mean bias of 0.45 for RASR and limits of agreement of 1.9 ($P = .002$).

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