JACC: CARDIOVASCULAR IMAGING VOL. 12, NO. 7, 2019

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Relative Left Ventricular Apical Sparing of Longitudinal Strain in Cardiac Amyloidosis

Is it Just Amyloid Infiltration?*

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Cardiac amyloidosis (CA) is a rare and phenotypically heterogeneous disease, with pathophysiological clinical and morphological variability. From an imaging point of view, CA is one of the cardiomyopathies with a hypertrophic phenotype and is frequently misdiagnosed on echocardiography as sarcomeric or idiopathic hypertrophic cardiomyopathy. However, there are morphological and functional features that could unravel the underlying myocardial infiltration, and relative apical sparing of longitudinal strain (LS) impairment is among the most specific and almost invariably reported findings.

Left ventricular (LV) apical sparing is a pattern of regional differences in deformation in which LS in the basal and middle segments of the left ventricle is more severely impaired compared with the LS values in the apical segments (1).

Apical sparing has been consistently observed in the 2 main types of CA: light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR) (2). Although a reduction in global LS is a common finding in any myopathic process that impairs myocardial contraction, apical sparing, although not pathognomonic, is highly specific for CA and has incremental diagnostic (2) and prognostic (3) value over other echocardiographic parameters traditionally used for this purpose.

Despite the extensive published reports focusing on apical sparing as a highly sensitive and specific sign for CA and its relatively widespread clinical use, the pathophysiological mechanism underlying apical sparing is unclear. At least 3 main mechanisms can be hypothesized: 1) less amyloid deposition at the apex rather than the base; it is in fact possible that with less amyloid deposition there is less resistance to deformation and, through a process of dynamic reciprocity, increased myocyte contraction, resulting in relative sparing of apical LS; 2) the greater diversity of myocyte and matric orientation at the apex compared with the base; this could potentially have a role in preservation of apical LS; and 3) greater tendency toward apoptosis and remodeling in the basal segments related to turbulent flow in the LV outflow tract and higher parietal stress.

The levels of evidence supporting these 3 hypothesis are different. Although several publications have reported a base-to-apex gradient in terms of amyloid deposition (by using histology, cardiac magnetic resonance [CMR], bone scintigraphy, and positron emission tomography [PET]) (4–6), no studies are available on the preferential involvement of specific fiber subtypes or the higher degree of apoptosis and remodeling at the base in CA.

In this context, one may question how the report by Bravo et al. (7) in this issue of *iJACC* adds anything other than incremental knowledge to the existing published reports that focused on assessment of the relationship between regional differences in LS and amyloid burden. The answer lies in the rigorous methodology, the multimodality approach, and the well-characterized study group. Bravo et al. (7) studied 32 patients with AL amyloidosis with echocardiography, to measure LS, and fluorine-18-florbetapir PET and CMR, to measure the amyloid fraction (LV florbetapir retention index [RI] and extracellular

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *iJACC* or the American College of Cardiology.

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ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2018.07.007

volume [ECV], respectively). These investigators found a significant base-to-apex gradient in LS, maximal wall thickness, and LV mass. No statistically significant differences were found in the amyloid fraction (florbetapir RI determined by PET and ECV determined by CMR), whereas markers of total amyloid load (total florbetapir binding and LV ECV) did show a statistically significant base-to-apex gradient. Bravo et al. (7) concluded that segmental differences in the distribution of the total amyloid volume, rather than the proportion of amyloid deposits, appear to explain the marked regional differences in LS in CA. The conclusion is in line with that of previous studies because this report confirms the association between regional differences in the distribution of amyloid deposits and regional differences in LS. However, this study adds a further nuance to this hypothesis by focusing on the role of total amyloid volume, rather than the proportion of amyloid, in determining apical sparing.

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One immediately evident critique is that other possible explanations for the regional differences in LS were not explored in this study. The study focused on the most extensively studied hypothesis (i.e., regional differences in amyloid load), thus leaving a knowledge gap on the role of other mechanisms. Although studying a greater tendency toward remodeling and apoptosis would require a histological approach, new CMR techniques have the potential to shed light on the role of differential involvement of specific fiber subtypes. The pixel-wise information derived by ECV mapping combined with diffusion tensor imaging could provide new insights into the role of differential involvement of subgroups of fibers with different orientation.

Moreover, only a subset of 22 patients underwent CMR with ECV measurement. This is a crucial subset within the report because the conclusion that focused on the importance of total amyloid load, rather than amyloid fraction, was made on the basis of the lack of statistically significant differences between the base and the apex in the florbetapir RI measured with PET and the ECV measured with CMR. There is a trend for a higher ECV at the base compared with the apex, and the lack of statistical significance in ECV could be related to the lower number of patients assessed with CMR (one-third less than those assessed with PET or echocardiography). Furthermore, ECV measurement was used (average across a region of interest), rather than ECV mapping (pixel by pixel quantification of ECV), and this could contribute to less discriminatory power for regional differences.

The work by Bravo et al. (7) is a cross-sectional study. We do not know how apical sparing develops with amyloid infiltration or whether it regresses when there is cardiac amyloid regression. We also do not know whether these patients were assessed before or after chemotherapy or, in patients assessed after chemotherapy, what the clonal response was. Recent studies have shown that CA is a very dynamic process, with clonal response being 1 of the most important factors driving changes in cardiac infiltration. Amyloid regression is not an uncommon phenomenon after successful suppression of the amyloid precursor, and amyloid progression can develop rapidly when there is no sufficient reduction in amyloid production (8). Studies assessing amyloid load and LS serially will be needed to address this important question.

Finally, only patients with AL amyloidosis were included in the study. The findings therefore should not be considered applicable to patients with ATTR amyloidosis.

In summary, what we learned from this report by Brave et al. (7) is that total amyloid burden seems indeed to be related to the differences in LS. The total amyloid volume was significantly higher at the base compared with the apex, as shown by a proportionally greater increase in LV mass that, in AL amyloidosis, is mainly driven by amyloid infiltration because there is no net gain in myocyte volume (9). It is, however, possible that not only regional differences in amyloid load but also multiple mechanisms, including the preferential involvement of specific fiber subtypes or the higher degree of apoptosis and remodeling at the base, form the pathophysiological basis of apical sparing. It is also possible that each of these mechanisms may be more or less prominent at any time point (before, during, or after chemotherapy in AL amyloidosis), depending on the individual patient (age, sex differences), the disease type (AL vs. ATTR), and comorbidities (hypertension, aortic stenosis). Apical sparing could therefore represent much more than the consequence of regional features in amyloid deposition, since it is probably the epiphenomenon of complex interactions among infiltration, anatomic structure, and myocardial adaptive and maladaptive responses.

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JACC: CARDIOVASCULAR IMAGING, VOL. 12, NO. 7, 2019
JULY 2019:1174–6

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KEY WORDS amyloidosis, extracellular volume, florbetapir, longitudinal strain, wall thickening