Quantitative molecular imaging of cardiac amyloidosis: The journey has begun

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Cardiac immunoglobulin light chain (AL) amyloidosis, an archetype of restrictive heart failure, has a median survival <1 year from onset of heart failure, if untreated.¹ While some therapies have proven highly effective for systemic AL amyloidosis, they have, unfortunately, also led to unacceptably high early treatment-related mortality in individuals with cardiac involvement.^{1,2} The gravity of this illness has motivated a surge in clinical trials of novel anti-amyloid therapies for AL and for transthyretin amyloidosis (ATTR, a more benign form of cardiac amyloidosis), the two most common forms of cardiac amyloidoses, in the hope of improving outcomes. Despite these positive steps, development of therapeutic breakthroughs for this disease is currently stalled because imaging advancements have lagged drug development. In fact, the lack of reproducible, validated, and quantitative in vivo imaging tools has become a major obstacle to the development of novel anti-amyloid therapies for the heart. This paper by Kero et al³ on C11-PIB imaging of cardiac amyloidosis

is an important first step in the journey toward solving this problem.

Cardiac amyloid burden can be assessed by structural imaging methods—echocardiography and cardiac magnetic resonance imaging (CMR). These modalities, however, are not specific for amyloidosis; also, echocardiography is suboptimal for detecting early disease or for serial imaging.^{4,5} Changes in myocardial wall thickness, measured by 2D echocardiography, typically lag clinical and biomarker improvement by a couple of years—a grave inadequacy for detecting response to therapy. CMR is a more powerful approach for tissue characterization than echocardiography. The higher sensitivity and reproducibility of late gadolinium enhancement, extracellular volume estimates,⁶ and myocardial T1 relaxation times,⁷ when compared to wall thickness measures, offer extraordinary promise for early disease detection and precise serial imaging. However, a recent phase two clinical study of a novel anti-TTR agent (Revusiran) did not report significant changes in myocardial structure (echocardiographic wall thickness), function (longitudinal strain), or tissue characteristics (left ventricular mass or ECV) at 90 days, despite apparently successful therapy achieving >80% reduction in serum TTR levels.⁸ For this reason, it is imperative to consider the potential advantages of functional positron emission tomography (PET) over structural imaging methods for cardiac amyloidosis. The unique ability of PET radiotracers to assess metabolic and molecular changes within tumors in response to molecular-targeted drugs, despite minimal changes in tumor size, has been established for cancer.⁹ Robust molecular imaging tools that signal early molecular changes may guide early drug modification or dose

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titration and prove vital to saving the lives of individuals afflicted with cardiac amyloidosis.

The Uppsala University group of investigators previously reported on the diagnostic value of manually calculated ^{11}C -PiB myocardial retention index (RI) to image cardiac amyloidosis in patients with documented AL and ATTR amyloidosis and in healthy controls. In the current paper, they extend the results of their first study by analyzing left ventricular (LV) myocardial retention of ^{11}C -PiB using semi-automatic software. They cleverly use a difference image, subtracting early ^{11}C -PiB blood pool images from later myocardial phase images, to outline the myocardial boundaries in the amyloid and normal subjects. Their results confirm that the semi-automatic method is simple and fast, and yields global and regional RI values that are strongly correlated with those obtained by manual methods. The semi-automatic method is also reproducible for global and regional RI, with excellent inter-reader reproducibility. Another important contribution of this paper is the segmental approach to quantitation, as well as histogram analyses to evaluate the distribution of radiotracer and parametric polar plots of the RI for simple visual assessment. As the authors point out, although most work to date has used global RI values, segmental quantitation to assess the distribution of amyloid may be critical to identify small changes in response to therapy which may not be revealed by global analyses. Ultimately, for detection of early cardiac amyloidosis, as well as for monitoring of changes in myocardial amyloid burden, as the authors acknowledge, full kinetic analysis with metabolite correction would be desirable. This study, which reanalyzes previously published data, is the first attempt at automatic software-based quantitation of cardiac amyloid burden; this approach to calculating RI is expected to decrease variability in the metric.

Four groups of investigators,^{10–13} including our own group, reported on the use of molecularly targeted amyloid tracers to diagnose cardiac AL and ATTR amyloidosis. Although each group used different metrics, all used semi-quantitative parameters.

Approaches to quantifying cardiac amyloidosis burden fall into three categories: semi-quantitative metrics derived from static images, semi-quantitative metrics derived from dynamic images, and parameters estimated from dynamic data by model-based analysis, either a graphical technique or full compartmental modeling. Approaches in the third category also require measurement of a blood- or image-derived input function, as do some approaches in the second category. The accuracy and precision of any semi-quantitative or quantitative parameter depends critically on the quality of the PET data; it is essential that these data are corrected for uniformity, detector dead time, random

coincidences, and photon attenuation and scatter. In addition, the reconstruction algorithm must be carefully chosen. Furthermore, although this has not yet been established, state-of-the-art PET systems with time-of-flight capability are likely to yield more accurate and precise metrics. Similarly, advanced reconstruction algorithms, such as those incorporating correction for the point-spread function, or 4-D direct parametric reconstruction approaches incorporating the temporal model, may lead to better quantitation.

The most commonly used metrics, target-to-background ratio (TBR) and standardized uptake value (SUV), fall into the first category. TBR, the ratio of myocardial tracer uptake (in Bq/mL or SUV) to blood pool activity or uptake in another reference organ, is a straightforward and easily interpreted measure, particularly for hot spot imaging; however, its value depends on the background selection.¹⁴ SUV, the ratio of radiotracer uptake in kBq/mL to the weight (or body surface area or lean body mass)-adjusted injected dose of radiotracer (kBq/g), is one of the most widely used quantitative metrics. SUV values are widely used in cancer imaging to distinguish benign from malignant lesions, to monitor response to therapy, and to define a metabolically active volume of tissue for treatment planning.¹⁵ SUV requires careful standardization, as it is subject to several sources of variability.^{15,16} Both SUV and TBR are influenced by the size and shape of the volume of interest, partial volume and spillover effects, image noise, time of evaluation relative to injection time, motion artifacts, and physiological state influencing myocardial radiotracer uptake.^{15,17} These limitations will also affect parameters estimated from dynamic imaging. For myocardial amyloid imaging, as for many other applications, SUV is an appropriate metric which has the advantages of being easy to measure and well established.

Metrics estimated from dynamic image series can, potentially, provide more information on physiology. Myocardial RI represents the proportion of the injected radiotracer dose that is retained by the myocardium. This quantity has been defined in several ways; the definition used by Kero et al is one of the more widely used: the ratio of the tissue activity over a given period (from 15 to 25 min) and the integral of blood activity from injection to the midpoint of that period, i.e., from 0 to 20 min.¹¹ The RI is more difficult to measure than are SUV or TBR, as dynamic image datasets must be acquired and analyzed; however, it is much simpler than kinetic analysis.

True quantitative analyses based on compartmental modeling¹⁸ provide much more detailed information about tissue function than do the semi-quantitative approaches discussed above, which could lead to high

discriminatory power between types of cardiac amyloidosis. Simpler graphical techniques, i.e., Logan analysis for reversible binding or Patlak analysis for irreversible binding, allow estimation of a limited number of parameters; these methods are relatively robust to noise. Full compartmental analysis yields estimates of several rate constants, reflecting, e.g., tracer diffusion between capillaries and tissue and binding properties, as well as quantities derived from them.¹⁸ Complex models may yield estimates of parameters that are much more sensitive to subtle differences in physiology; however, estimating multiple parameters from noisy data is inherently unstable and may lead to imprecise estimates. Ideally, full kinetic analysis involves multiple arterial blood samples for measurement of the (plasma) input function, as well as, for some tracers, correction of the input function for metabolites.¹⁸ Image-derived input functions using a larger artery or LV blood pool are often substituted for blood sampling; with this approach, it is not possible to measure metabolic activity in individuals. In some cases, metabolite correction based on population-averaged data can be used.

Although cardiac amyloidosis is easily diagnosed by visual scan interpretation, semi-quantitative metrics based on static or dynamic imaging are necessary for tracking disease severity or changes. Moreover, full compartmental modeling may be necessary for the detection of early disease or small changes in amyloid burden. But full compartmental modeling is cumbersome and not feasible for routine clinical practice. The role of full compartmental analysis studies may be to validate the simpler metrics (not requiring blood sampling), for use in clinical practice.

CONCLUSIONS

Recent developments in novel therapies and amyloid binding PET radiotracers present a potential breakthrough for precise imaging guided management of cardiac amyloidosis. The development of quantitative methods for cardiac amyloidosis imaging must be accelerated to match the pace of drug development efforts. Standard methodology, as emphasized by Kero et al,³ and collaborative effort are crucial for research into rare diseases such as cardiac amyloidosis, so that data can be pooled. Advances in quantitative molecular imaging of amyloidosis are paramount to transform the outcomes of individuals afflicted with cardiac amyloidosis. The journey has begun.

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