

## EDITORIAL COMMENT

# There Is More Than Shape and Function\*

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*"Most things break, including hearts. The lessons of life amount not to wisdom, but to scar tissue and callus."*

—Wallace Stegner, *The Spectator Bird*, 1976 (1)

*Cardiac arrhythmia due to cardiac hypertrophy with patchy fibrosis of undetermined etiology. Natural Causes.*

—autopsy report of Ryan Shay, marathoner (1979–2007) (2)

Heart failure has become our most important health care concern. Although drug therapy has made impressive advances, the prognosis of patients with symptomatic heart failure remains poorer than that of most malignant diseases (3). Therapeutic decisions are typically based on large-scale trials instead of on the individual patient.

The lack of personalized treatment stems from the absence of clinical tools for accurately phenotyping patients with heart failure. The understanding is largely limited to symptoms and findings of the physical examination, combined with data on morphology and contractile function of the heart. Albeit useful in several clinical scenarios, this information is of little help in developing disease-specific therapeutic strategies.

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Among serologic biomarkers, brain natriuretic peptide (BNP) is useful for taking an accurate snapshot of the current severity of pressure overload, but is nonspecific regarding the underlying disease. Inflammatory markers, though of prognostic value (4), are not specific to myocardial disease, and their clinical role in heart failure remains to be established. Furthermore, they do not provide relevant information on the reversibility of myocardial injury or disease-related therapeutic targets.

Myocardial tissue composition holds a lot of important information on disease-specific patterns of injury, current activity of disease-related mechanisms such as inflammation, and the reversibility of changes. Fibrosis is the main feature of chronic tissue damage in heart disease. Myocardial infarction is the most prevalent example, and the extent of fibrosis is the most accurate marker of injury severity.

Endomyocardial biopsy can be used to assess tissue abnormalities such as fibrosis, but its utility in most clinical scenarios is limited by its invasiveness and its low sensitivity to detect regional pathology. Certain biochemical markers are associated with fibrosis and appear promising (5). Current data, however, are largely experimental and there are concerns about the specificity for myocardial fibrosis. Thus, a tool for identifying the presence and quantifying the extent of myocardial fibrosis would enable us to gather important diagnostic and prognostic information in patients with heart failure.

The paper by Iles et al. (6) in this issue of the *Journal* describes a novel approach to identify and quantify diffuse fibrosis using cardiovascular magnetic resonance (CMR) imaging. Using measurements of the longitudinal proton relaxation time ( $T_1$  mapping) in post-contrast CMR images, the authors provide evidence, in patients with heart failure of various etiologies, that global  $T_1$  is significantly shorter than that in a control group. This effect correlated well with markers of diastolic function and—in a small subset of patients with biopsy—with the histologic amount of tissue collagen.

There are some limitations to the study: it suffers from a very small sample size of subjects with histologic correlation and does not address potential confounders of gadolinium distribution such as renal function, cardiac output, injection rate, and—most importantly—timing of image acquisition after contrast administration. Furthermore, sequence parameters and the applicability for different hardware have to be tested. Moreover, the data will have to be reproduced and the added value for individual phenotyping further addressed.

But even with these limitations, this work is important, providing clinical proof of a concept for using basic magnetic properties of protons—components of virtually all metabolites—for in vivo assessment of tissue pathology.

Many cardiologists have yet to embrace the concept of tissue characterization in clinical decision-making, and imaging in patients with heart failure is still very much focused on cardiac shape and function. Ventricular volumes and contractility, however, may be misleading in some clinical settings. The 2 ends of the cardiac phenotype spectrum may be best represented by a patient with normal ejection fraction but heart failure due to myocardial restriction and low cardiac output, versus a healthy endurance athlete with low ejection fraction and eccentric hypertrophy. Thus, there is a need for more sophisticated imaging tools for accurate individual phenotyping.

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Among currently available imaging modalities, magnetic resonance imaging (MRI) stands out because of its accurate quantitative data, but more so due to its unique image-generating physics, which make it especially suitable for tissue characterization. MRI signal intensity is based on relaxation properties of protons in the static magnetic field of a scanner. Since these properties depend on the molecular environment, MRI can make use of an inherent contrast between different tissues. Without using tracers or contrast agents, specific protocols of high-frequency pulses ("sequences") are used to generate images with a specific tissue appearance. This can be used for diagnostic tissue characterization, for example, looking for tissue degeneration in arrhythmogenic right ventricular cardiomyopathy (7,8) or myocardial edema in acute myocardial injury (9,10).

Contrast-enhanced CMR imaging is already being used to detect tissue abnormalities and works through a regionally increased volume of distribution. Gadolinium-based agents are primarily interstitial agents and, after an initial wash-in, enter a brief (minutes) steady state with parallel wash-in and wash-out into and from interstitial space. The contrast-generating mechanism of gadolinium is based on the acceleration of proton relaxation times and a subsequent increase of regional signal intensity in  $T_1$ -weighted images. This change can be observed in diseases such as myocarditis, with regionally increased blood volume and capillary leakage (11,12).

Necrosis and fibrosis are characterized by a substantial increase in the interstitial volume of distribution for gadolinium compounds, particularly by a significant delay of their washout. If CMR images are acquired late (i.e., between 5 and 30 min) after gadolinium administration, the agent will have been washed out from predominantly normal tissue, but will remain in regions with irreversible injury (13). Using a specific parameter setting (a selective frequency pulse, which suppresses the magnetic resonance signal of normal myocardium), gadolinium-accumulating ("enhancing") regions can be sensitively detected. This technique, called "late gadolinium enhancement" or "delayed enhancement," is the gold standard for the noninvasive assessment of infarcts and is increasingly used for assessing myocardial viability (14). The degree of late enhancement appears to predict functional outcome after revascularization (15) and future clinical events (16). Although it is a nonspecific result of any injury involving violent cell death, its regional distribution holds information on the underlying etiology of myocardial disease (e.g., ischemic, inflammatory, infiltrative, degenerative) (17-20).

Late gadolinium enhancement CMR, however, is limited not only by coil reception properties, field inhomogeneities, and artifacts, but especially in patients with predominantly global, diffuse myocardial fibrosis. Because apparently normal myocardium is needed to define the parameter setting that best suppresses its signal, it is difficult to quantify the extent of myocardial fibrosis if most of the tissue is affected or if there is limited "normal" myocardium. Because the

parameter settings are "tuned" to partially fibrotic myocardium, high signal intensity may not be present, despite a globally increased gadolinium concentration.

This gap could be filled in heart failure patients, as suggested by Iles et al. (6), because it allows for identification of a uniform or only slightly varying regionally different abnormal gadolinium uptake. The idea to measure proton relaxation time itself instead of signal intensity to detect tissue pathology is not new. In fact, as the first medical application of magnetic resonance, Damadian (21) measured  $T_1$  to identify malignant tumors. But technical difficulties and lengthy protocols prevented the clinical use of this approach. Improved hardware and software protocols are now available (22,23) and facilitate the use of mapping  $T_1$  relaxation for clinical purposes in myocardial infarction (24) and amyloidosis (25). Initial reports on normal values and reproducibility indicate a reasonably small scatter to allow for defining cut-off values for clinical decision-making (26). A broader use of this approach, however, requires more data, both in the normal and diseased populations, as well as standardized sequences and protocols. This has to consider contrast agent properties such as concentration, relaxivity, and wash-in/wash-out characteristics. Furthermore, cardiac output, injection route, and rate have to be addressed as potential confounders (input function). Potential solutions for these issues, such as automatic triggering and internal normalization, are available.

The study by Iles et al. (6) is the first report on the use of  $T_1$  mapping in phenotyping patients with heart failure, and the authors should be congratulated for addressing an important diagnostic target. If confirmed in larger samples,  $T_1$  mapping may be useful in patients with heart failure as part of a comprehensive CMR study, providing information on cardiac size, morphology, function, valvular function, and tissue characteristics. Such a scan, acquired in less than 30 minutes, not only is safe and very informative, but is also a very cost-efficient diagnostic test and allows for correlating multiple aspects of the disease at the very same stage of disease.

Still perceived as complex by some, CMR already provides a uniquely wide spectrum of diagnostic targets in cardiac diseases. It is now up to the industry and professional societies to develop and implement streamlined protocols, simple and fast scanning procedures, accurate post-processing algorithms, and suitable evaluation tools for tissue characterization.

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**Key Words:** cardiovascular magnetic resonance ■ heart failure ■ dilated cardiomyopathy ■ tissue characterization ■ fibrosis ■ late gadolinium enhancement ■ T1 mapping ■ edema.