

# Heart failure and cardiac imaging: Choosing wisely in the era of multimodality imaging

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## Introduction

Heart failure is the common final outcome of many heart diseases. Cardiac imaging plays a central role in its diagnosis and etiological work-up. Given the large array of imaging modalities, as well as structural and functional parameters, devising a diagnostic strategy that provides diagnostic accuracy without wasting resources can be challenging. “Multimodality imaging” has become a popular buzzword without a clear meaning, except for different modalities showing different aspects, which sometimes may be helpful and sometimes not. Is multimodality imaging *per se* diagnostically superior? When should we escalate from echocardiography to other modalities? In this viewpoint article, we attempt to provide guidelines on the rational deployment of modern imaging armamentarium in heart failure.

### The role of echocardiography in the diagnosis of heart failure

In patients with symptoms suggestive of heart failure, after the history taking, physical examination, electrocardiogram evaluation, and perhaps drawing blood for natriuretic peptides, the next diagnostic step is unquestionably an echocardiogram (1, 2). This can usually – unless in special circumstances, such as forbidding acoustical windows – address the following fundamental questions:

- What are the left ventricular size, ejection fraction, and global longitudinal strain?
- Are there signs of diastolic left ventricular dysfunction?
- Are there regional wall motion abnormalities suggesting coronary artery disease (CAD)?
- Is there left ventricular remodeling or hypertrophy?
- Is there (major) valvular heart disease?

- Are there structural abnormalities suggesting cardiomyopathy?
- Are there right ventricular abnormalities, congenital heart disease (e.g., atrial septal defect), or other major structural abnormalities?

The echocardiographic answers to these questions usually allow, together with other clinical information, to arrive at least at a tentative diagnosis and to start therapy. In some cases, standard echocardiography should be enhanced by left heart contrast (e.g., to better see the apex of the left ventricle) or by transesophageal echocardiography (e.g., to rule out an atrial septal defect, especially a sinus venosus defect). Diastolic function assessment and strain imaging provide additional important clues for the diagnosis of heart failure. For example, hypertrophic cardiomyopathy is often characterized by extremely low E and e' values because of massively disturbed relaxation, especially in the hypertrophied septum. Conversely, advanced diastolic dysfunction (restrictive transmitral profile) is typically observed in amyloidosis, which is also characterized (although not uniquely so) by the apical sparing pattern of the longitudinal strain. In addition, Anderson-Fabry disease as well as cardiac sarcoid may be associated with localized deterioration of strain, which may not be noticeable to the naked eye. Importantly, strain imaging can detect myocardial disease in the ventricles with preserved ejection fraction, and reduced global longitudinal strain (GLS) predicts the prognosis of these patients (3). The high sensitivity of reduced GLS for the incipient heart failure has further led to its integration in screening protocols for the cardiotoxicity of cancer chemotherapy and may in the future aid in better defining the beginning of heart failure in patients with severe valvular disease. However, diastolic LV function disturbances and strain

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reductions are functional, quite unspecific “red flags,” indicating a myocardial disease, but not which one.

Thus, echocardiography (perhaps combined with coronary angiography) seemed to provide all necessary information in heart failure, except for myocarditis, sarcoidosis, and others, which essentially required myocardial biopsy for a more accurate diagnosis. However, cardiac imaging has undergone rapid and diverse development over the last decades, and increasingly, we must recognize that this traditional approach is incomplete and will lead to missed diagnoses if current diagnostic possibilities are not explored (Table 1). Simultaneously, it is important to “choose wisely,” as the American College of Cardiology (4) has launched a campaign to contain the overuse of imaging, and thereby, strengths and weaknesses of the imaging modalities at our disposition should be understood.

### The new players in the imaging arena

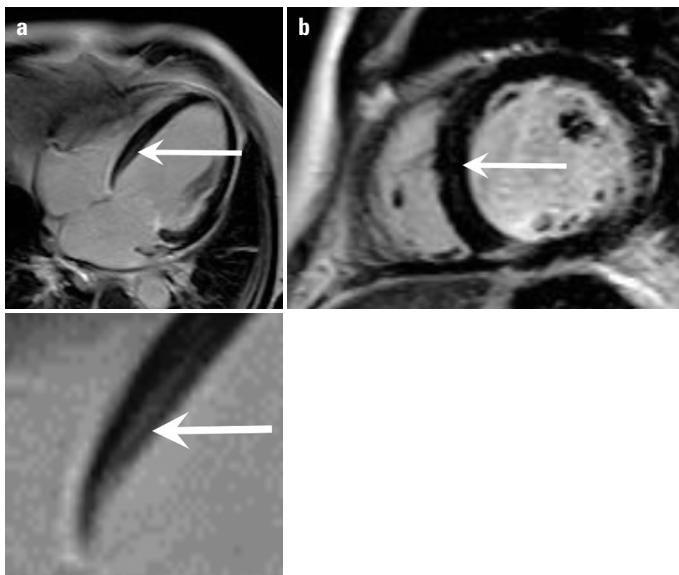
Cardiovascular magnetic resonance (CMR) is the most versatile “advanced imaging” modality. Beyond its more precise and reliable measurement of volumes and ejection fraction of both chambers, than echocardiography, the great strength of CMR is its ability to characterize the tissue. This is not the same as histology, but still allows a far better understanding of myocardial tissue changes than all other modalities. After gadolinium contrast application, localized increased extracellular space (ECV) can be identified as “late gadolinium enhancement” (LGE). These localized increases occur from replacement

fibrosis after a myocardial infarction. Subendocardially located late gadolinium enhancement in the perfusion territory of a coronary accurately identifies and quantitates infarct scars. However, LGE can also be found in typical patterns with myocarditis (Fig. 1), cardiomyopathies, and cardiac storage diseases like amyloidosis, and is associated with the prognosis and therefore a very useful diagnostic feature. A further major advancement in tissue characterization by CMR has occurred through quantitative pixel-by-pixel determination (so-called parametric mapping) of the relaxation time constants (in milliseconds) T1, T2, T2\*, and the estimate of ECV (in percent), which can be measured using the pre-contrast and post-contrast T1. These parameters reflect both extra- and intracellular tissue features, related to the chemical composition of the tissue, and thus provide clues as regards the amount of water in the myocardial tissue (e.g., inflammation and edema), the presence of large molecules (e.g., sphingolipids in Anderson-Fabry disease), iron, and other factors (5-8). They provide time constants in absolute values, not just gray levels in the image, and therefore also can identify diffuse changes, such as in generalized fibrosis, which LGE cannot visualize. Relaxation times and ECV cannot unambiguously identify specific diseases or histologies. However, for some diseases, the “signature” can be quite characteristic, such as amyloid (Fig. 2) with long T1 and Anderson-Fabry disease with very short T1 times (at least in early disease) or hemochromatosis with shortened T2\* times. Although the methodology is machine and protocol dependent and subject

**Table 1. Newly detected heart failure: factors and mechanisms to be ruled out/in. Modified from Krister Lindmark, Umeå, Sweden**

	Recommended imaging test(s)	Other helpful tests in addition to history taking, physical exam, and ECG
Hypertensive heart disease	Echo	
CAD	(Echo), CT, ischemia testing	
Valvular heart disease	Echo, (CMR)	
Tachycardia (ventricular or supraventricular)	Echo	
Hypertrophic cardiomyopathy	Echo, CMR	Genotyping
Hypothyroidism	Echo	Laboratory
Myocarditis	CMR	Laboratory (troponin, virus serology), biopsy
Hemochromatosis	CMR	Laboratory
Hereditary dilated cardiomyopathy	Echo, CMR	Genotyping
Cardiac amyloidosis	(Echo), SPECT, PET, CMR	Biopsy, laboratory (for light-chain amyloidosis)
Andersen-Fabry	(Echo), CMR	Laboratory
Sarcoidosis	CMR, PET	Laboratory (angiotensin-converting enzyme), biopsy
Postpartum cardiomyopathy	Echo	
Chemotherapy	Echo, CMR	
Drug toxicity	Echo	Laboratory
High alcohol intake	Echo	Laboratory (phosphatidylethanol)

CMR - cardiovascular magnetic resonance; CT - computed tomography; PET - positron emission tomography



**Figure 1.** Cardiovascular magnetic resonance midwall enhancement in dilated cardiomyopathy. A 57-year-old man with dilated cardiomyopathy and thin septal midwall enhancement (arrows). Top left, four-chamber view, top right, short axis view. Ejection fraction, 23%; LV end-diastolic volume, 188 mL/m<sup>2</sup>; generalized hypokinesia. Bottom: magnification Fig. 1a for better visualization of midwall enhancement in basal septum

to many possible errors, the parametric imaging constitutes a major advancement in cardiac imaging and the closest we can come with “virtual histology” today. Limitations and contraindications of CMR apply, such as an image deterioration with arrhythmia, renal impairment for gadolinium contrast application, non-compatible cardiac implants like some pacemakers, and claustrophobia.

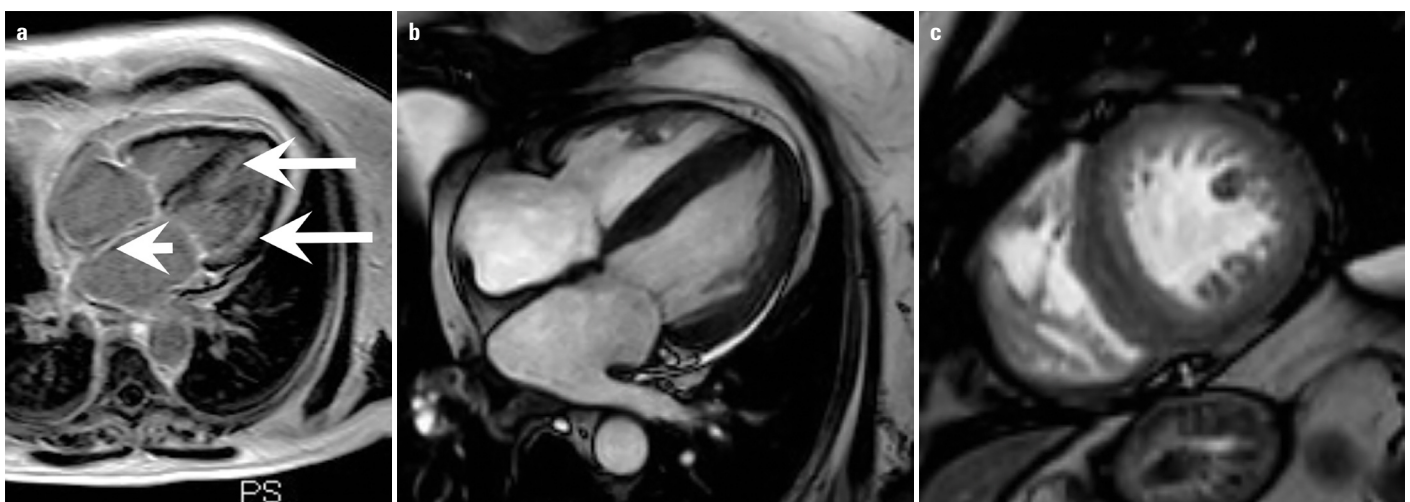
Other very important new players are cardiac computed tomography (CT). Its main task is the exclusion of coronary artery disease by noninvasive coronary angiography, and the stratifica-

tion of cardiovascular risk by quantifying coronary calcification, typically using the Agatston score. Although the latter is only indirectly related to heart failure, information on cardiovascular risk and CAD extent is indispensable for the management of patients with heart failure. CT is also limited in the presence of atrial fibrillation or renal impairment and involves radiation exposure.

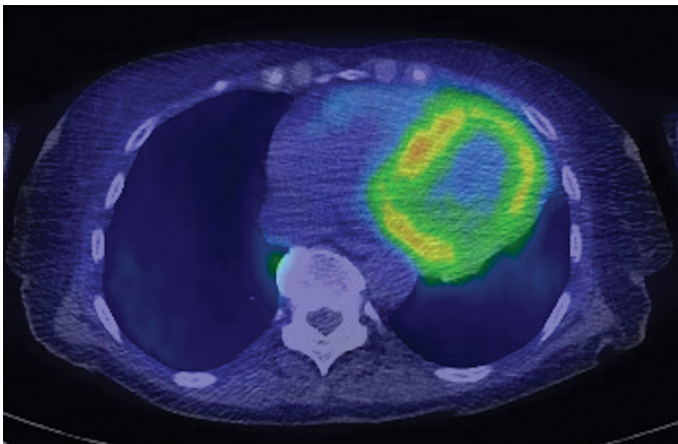
Remarkably, both CMR and CT also permit determination of myocardial strain, although this is still a research tool to date.

The third modality increasingly involved in the diagnostic work-up of patients with heart failure is nuclear imaging. Apart from its classic function of identifying permanent or stress-inducible myocardial perfusion defects as signs of CAD, it has several unique applications in the field of heart failure, most importantly:

- 1) <sup>99</sup>Tc-diphosphonate SPECT, used traditionally in identifying sites of high bone metabolism (“bone scan” for bone metastases), visualizes cardiac transthyretin amyloidosis.
- 2) Positron emission tomography (PET) can determine absolute regional myocardial perfusion and perfusion reserve and provide functional information about both epicardial coronary and small-vessel function.
- 3) PET can also be used to assess myocardial viability by detecting low regional perfusion areas but preserved metabolism (“mismatch”), separately measuring perfusion and metabolism using different tracers.
- 4) PET can detect all types of cardiac amyloidosis (9) using specific ligands, e.g., <sup>11</sup>C-PIB (Fig. 3) and help diagnose cardiac sarcoidosis by visualizing cardiac areas of high metabolism corresponding to sarcoid granulomas (10).
- 5) PET assessment of how well the myocyte transforms chemical into mechanical energy (myocardial external efficiency; 11), up to now still a research area.



**Figure 2.** Cardiovascular magnetic resonance images of a 69-year-old man with cardiac amyloidosis. a) generalized subendocardial LGE, including the atrial walls. Thickened atrial septum and pericardial effusion. LV end-diastolic volume, 67 mL/m<sup>2</sup>; LV EF, 46%; and LV mass, 68 g/m<sup>2</sup> (normal). Septal native T1 1140 ms (increased), ECV 57% (massively increased). Late gadolinium enhancement image (four-chamber view) with diffuse LV subendocardial enhancement (arrows); note also interatrial septum thickening (short arrow) and pericardial effusion. b and c) Diastolic cine (steady-state free precession) frames (b, four-chamber view, c, short-axis view), showing increased wall thickness as the only pathology



**Figure 3.** A 75-year-old female patient with light-chain (AL) amyloidosis. CT-PET with  $^{11}\text{C}$ -PIB (courtesy Jens Sørensen, PET center, Uppsala University) showing a diffuse uptake of the radioisotope in the left ventricle

Nuclear methods involve, sometimes considerable, radiation exposure, but have little other limitations or side effects.

### How to put it all together

Obviously, echocardiography remains the first and often the only modality necessary to capture an image of the failing heart. However, some diseases leading to heart failure may not allow a clear diagnosis in the echocardiogram, such as myocarditis, early stages of cardiomyopathies, and storage diseases, apart from the important limitation of suboptimal echocardiographic image quality, e.g., in obese patients. Limitations of echocardiography in this scenario can be summed up in three categories:

- 1) CAD. In the absence of well-defined resting regional wall motion abnormalities that can be assigned to coronary perfusion territories, an ischemic disease cannot be ruled out. However, stress echo has a high positive predictive value for CAD, but the negative predictive value is quite limited; hence, the method requires substantial expertise. Nowadays, not only flow-limiting coronary stenoses but also about non-flow limiting plaques and the presence of small-vessel disease should be considered. CT can not only exclude flow-limiting coronary lesions, but additionally provide quantitative information on coronary atherosclerotic plaque burden, which has implications for further CAD prevention (e.g., statin use). Furthermore, PET provides the best quantitative regional myocardial perfusion and perfusion reserve data reflecting myocardial small-vessel and capillary vascular beds.
- 2) Heart failure with reduced ejection fraction (HFrEF). Even after ruling out CAD, a spectrum of etiologies still exists, some of them treatable, which cannot be differentiated by echocardiography. This ranges from myocarditis to familial dilated cardiomyopathies, sarcoidosis, hemochromatosis, and others. In this context, CMR allows to:
  - Identify typical patterns of localized replacement fibrosis by late gadolinium enhancement such as “midwall enhance-

ment,” with established diagnostic and prognostic implications

- Identify myocardial edema, such as in myocarditis, by conventional techniques including fat-suppression sequences (e.g., T2wSTIR) or by T1 and T2 mapping;
  - Identify pathologic myocardial storage of substances, e.g., iron in hemosiderosis, which may mimic dilated cardiomyopathy.
- 3) Heart failure with preserved ejection fraction (HFpEF). This condition is typically caused by hypertension and involves LV concentric remodeling or concentric hypertrophy, although other remodeling patterns exist in hypertension (12). However, other diseases may also cause thickened LV walls, most prominently hypertrophic cardiomyopathy and cardiac amyloidosis. Amyloidosis may not be associated with pronounced wall thickening in its early stages. In a study where all HFpEF patients with a septal thickness  $>14$  mm were systematically subjected to a  $^{99}\text{Tc}$  diphosphonate scan, 13% of them were diagnosed with cardiac amyloidosis, which had not been suspected clinically before (13). Cardiac amyloidosis can also be detected with high accuracy by PET (all forms of amyloidosis) and SPECT (mainly transthyretin amyloidosis) and can also be diagnosed (although less specifically) by CMR through LGE and increased T1 as well as ECV values. Lastly, CMR or CT provides more reproducible and robust data on LV and RV volumes and ejection fraction than echocardiography and can thus help in early cancer therapy-induced cardiotoxicity of the anthracycline type or in phenotypic borderline cases of arrhythmogenic cardiomyopathy.
- Thus, contemporary imaging modalities offer striking diagnostic capabilities, which approach a “virtual myocardial histology.” They can detect amyloidosis, Anderson-Fabry, sarcoidosis, and hemochromatosis, diseases proven with treatment options. Even in diseases without clear treatment options, such as myocarditis or cardiomyopathies, decisions regarding follow-up or screening of relatives may be better informed by specialized imaging. Having a diagnosis is also a value in itself, for the patient and her/his family, and additionally may spare the patient and the healthcare system insignificant further diagnostic efforts. However, do we need to perform CMR, SPECT, or PET in each patient with heart failure and increased LV wall thickness? Probably not, if there is a good causal explanation (e.g., hypertension) and the course and clinical picture do not suggest another etiology, or if the benefit from treatment is unlikely, such as in the very old and multimorbid.
- Recognizing that terms like “dilated cardiomyopathy” or “concentric hypertrophy” are relatively crude and may mask more specific, potentially treatable underlying diseases will change the practice of care for patients with heart failure (14). Therefore, we should be familiar with the possibilities afforded by the new modalities, even if they are costly and not always available. They are not infallible and do not invalidate echocardiography, which remains the most important imaging tool; however, they can be used as additional methods to help our patients.

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