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CURRENT OPINION

Non-invasive cardiac imaging evaluation of patients with chronic systolic heart failure: a report from the European Association of Cardiovascular Imaging (EACVI)

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Introduction

In patients with heart failure (HF) and reduced ejection fraction (EF), non-invasive cardiac imaging provides diagnostic, prognostic, and therapeutic information and assists decision-making. The aim of this consensus paper is to provide an overview of the clinical applications of non-invasive cardiac imaging in the management of HF patients with systolic dysfunction, mostly focusing on impact on clinical decision-making (*Figure 1*).

Diagnosis

In patients with suspected HF, an electrocardiogram, chest X-ray, and brain natriuretic peptide (BNP or NT-proBNP) assay should be performed before non-invasive cardiac imaging,[1] but in particular clinical situations with high likelihood of the disease, i.e. symptoms of HF in patients with previous myocardial infarction, cardiac imaging might be directly performed without previous BNP assay.

Left ventricular (LV) systolic dysfunction, conventionally identified when EF at rest is <50%, is detected in ~50% of patients with HF. However, EF does not accurately reflect the contractile status of the myocardium as it is influenced by loading conditions. In addition, EF does not reflect cardiac output that can be preserved in patients with low EF but large left ventricle, or decreased in patients with normal EF but reduced LV chamber size or impaired diastolic function or severe mitral regurgitation. Additional parameters that are usually abnormal in patients with systolic HF include increased end-diastolic diameter and volume (LV diameter >60 mm or 32 mm/m^2 with LV volume >97 mL/m^2) and end-systolic diameter and volume (LV diameter >45 mm or 25 mm/m^2 with LV volume >43 mL/m^2).

To measure these parameters and establish the diagnosis of systolic HF either an echocardiogram or cardiac magnetic resonance (CMR) at rest should be performed.[1]

Using echocardiography, EF should be calculated adopting the apical biplane rule (modified Simpson rule), with the use of contrast agent when <80% of the endocardial border is visualized, whereas visual assessment of EF is not recommended.[2] However, clinicians should be aware of the suboptimal reproducibility of echocardiographic EF measurement[3] and rely on examinations performed by experienced operators. Although still not widely diffused, three-dimensional echocardiography improves reproducibility of EF measurement.[2]

Left ventricular systolic function can also be assessed measuring atrioventricular plane systolic excursion, systolic tissue Doppler velocities, and deformation indexes, including strain and strain rate. Although abnormalities of these indexes precede EF decrease, and might be more sensitive to identify pre-clinical HF,[4] their use in clinical practice is still limited due to reduced reproducibility and lack of standardization.

Echocardiography allows accurate evaluation of LV diastolic function that is commonly impaired in patients with reduced EF.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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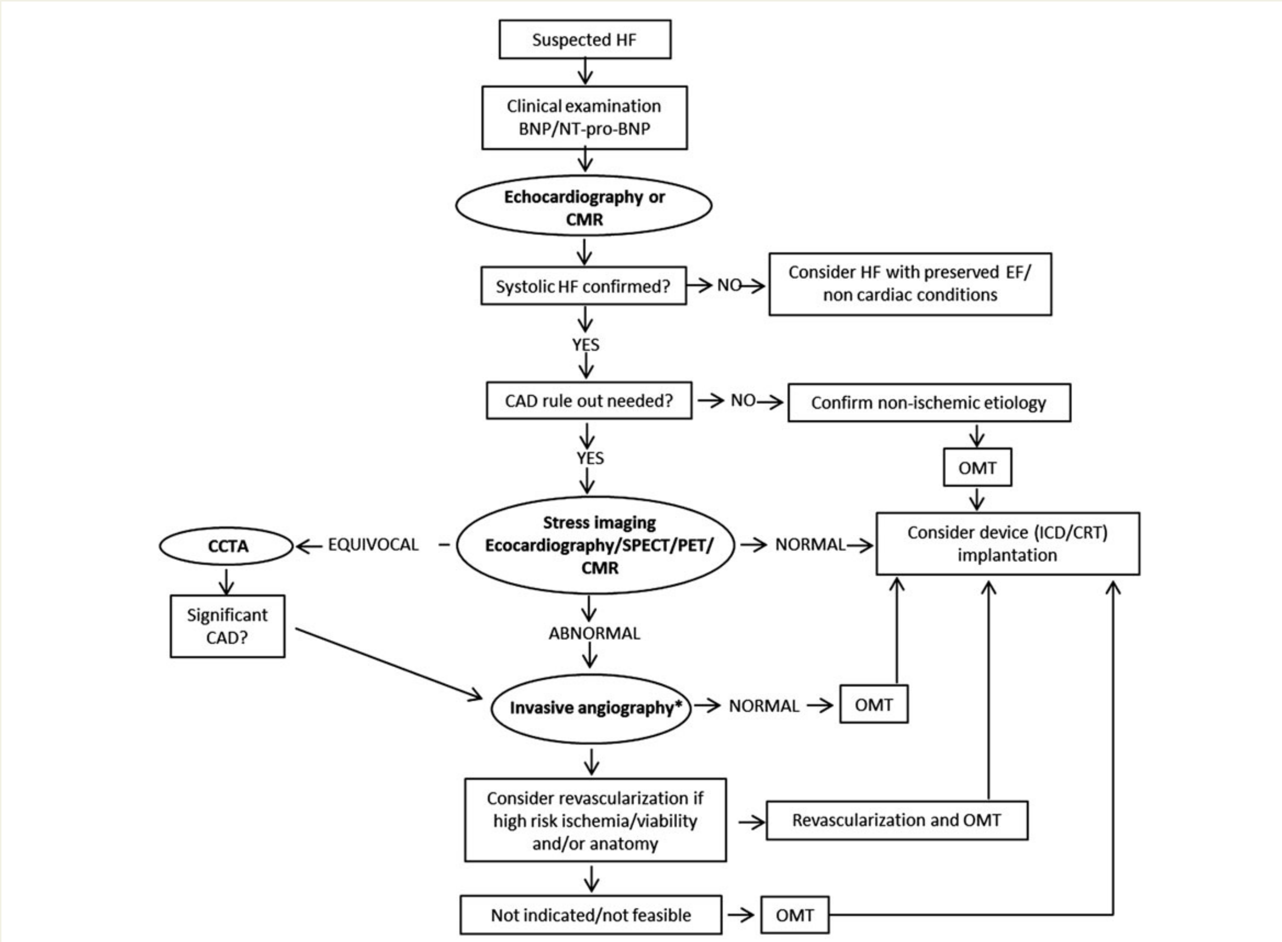

Figure 1 Use of cardiac imaging for the management of patients with chronic systolic heart failure. HF, heart failure; BNP, brain natriuretic peptide; CMR, cardiac magnetic resonance; EF, ejection fraction; CAD, coronary artery disease; CCTA, cardiac computed tomographic angiography; SPECT, single photon emission computed tomography; PET, positron emission tomography; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; OMT, optimal medical therapy. *might precede stress imaging in patients with angina.

Guidelines recommend a comprehensive evaluation of echocardiographic and Doppler parameters, to assess LV mass, left atrial dilation, and functional diastolic indexes. These latter should include tissue Doppler imaging-derived early diastolic myocardial velocities (e') (normal >8 cm/s septal, >10 cm/s lateral, or >9 cm/s average) that reflects myocardial relaxation and the E/e' ratio (normal <15) that reflects filling pressure. The mitral inflow E/A ratio (normal 1–2) identifies the pattern of diastolic dysfunction (restrictive if >2, impaired relaxation if <1 or 'pseudonormal' if between 1 and 2 but decreasing >0.5 during the Valsalva maneuver) providing insights into the loading conditions of the left ventricle that can assist therapeutic management.

Cardiac magnetic resonance is the most valuable alternative to echocardiography and represents first-line technique in patients with unfavourable acoustic window, like those with pulmonary diseases, or in patients with complex congenital diseases, or in patients in whom characterization of myocardial tissue is needed (see below). At variance with echocardiography, measurements are independent on geometric assumptions, making CMR the gold standard technique for the assessment of EF and LV volumes[5] (*Figure 2*). In addition, the right ventricle can be accurately evaluated and, by combining cine and flow-sensitive CMR imaging, valvular regurgitation and intracardiac shunt volumes can be quantified.[5]

However, lack of portability, reduced availability, and higher costs are current limitations to the use of CMR. In addition, CMR cannot be performed in claustrophobic patients or in patients with severe renal impairment (>IV renal disease stage), in whom administration of gadolinium is contraindicated for the risk of nephrogenic systemic fibrosis.[6] Increased use of CMR compatible pacemakers will progressively reduce the number of patients hosting devices precluding CMR, but implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) remain a contraindication in many patients with HF.[7]

Cardiac computed tomography (CCT) allows quantification of LVEF and volumes that can be achieved using a spiral mode with image data acquisition throughout the entire cardiac cycle, leading to higher radiation exposure, or acquiring both systolic and diastolic phases with step-and-shoot protocol, with modest radiation dose increase.[8] However, CCT has currently limited role to assess cardiac function in patients with suspected HF.[1]

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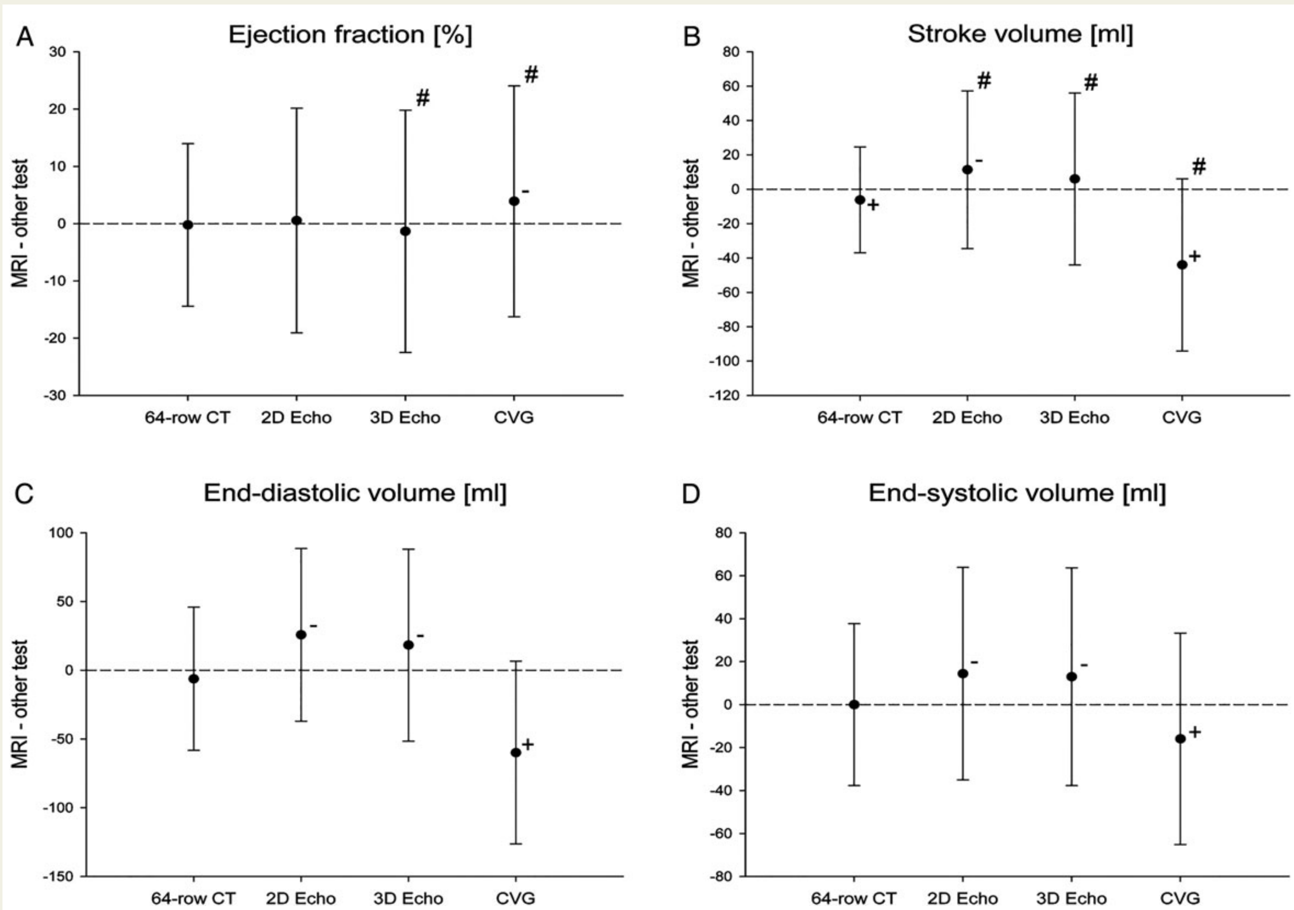

Figure 2 Head-to-head comparison of left ventricular function assessment with 64-row computed tomography (64-row CT), biplane left cineventriculography (CVG), and two- and three-dimensional transthoracic echocardiography (2D Echo; 3D Echo), using cardiac magnetic resonance (CMR) as the reference standard. The results of Bland–Altman analysis of intermethod agreement for left ventricular ejection fraction (EF) and volumes, conducted on 36 patients who underwent 64-CT, CVG, 2D Echo, 3D Echo, and CMR studied by Groupier *et al*., are shown. The mean difference of CMR and index tests is represented by circles with their limit of agreement (95% confidence interval, ± 1.96 SD). Sixty-four-row CT did not overestimate or underestimate EF (*A*), end-diastolic volume (EDV) (*C*), or end-systolic volume (ESV) (*D*) in comparison to CMR, but significantly overestimated stroke volume (SV) (*B*). CVG significantly overestimated all left ventricular volumes (*B* to *D*), and 2D Echo and 3D Echo showed a significant underestimation of EDV (*C*) and ESV (*D*), whereas SV was significantly underestimated by 2D Echo (*B*). CVG and 3D Echo showed significantly larger limits of agreement ($P < 0.05$) than 64-row CT for EF (*A*) and SV (*B*), whereas for EDV (*C*) and ESV (*D*) there was no significant difference. For 2D Echo, limits of agreement were larger for SV, but not for EF (*A*) and volumes (*C* and *D*). From Greupner *et al*.[5] + = significant ($p < 0.05$ overestimation vs. MRI); − = significant ($p < 0.05$ underestimation vs. MRI); # = significantly larger limits of agreement vs. 64-row CT.

Assessment of LV function is also recommended in asymptomatic patients with known or suspected coronary artery disease (CAD) in current guidelines (Class I, level of evidence A)[9] and in patients undergoing chemotherapy.[10] In this latter category, chemotherapy should not be initiated or should be suspended when EF $\leq$ 44% or a significant decrease ($>$10 points from baseline) during the course of therapy.

Aetiology of heart failure

Heart failure with reduced EF can be due to several pathological conditions, including idiopathic dilated cardiomyopathy, valvular, hypertensive and ischaemic heart disease, toxin-induced cardiomyopathies (e.g. doxorubicin, herceptin, alcohol), as well as congenital heart disease. Right ventricular systolic dysfunction is usually a consequence of LV dysfunction, but can also develop as a result of right ventricular infarction, pulmonary hypertension, chronic severe tricuspid regurgitation, or arrhythmogenic right ventricular dysplasia.

Coronary artery disease accounts for two-thirds of HF due to LV systolic dysfunction and is associated with increased mortality compared with non-CAD aetiology.[11] Ischaemic LV systolic dysfunction is diagnosed in patients with a history of myocardial infarction or angiographic evidence of CAD.[11] Invasive coronary angiography has long been considered the gold standard to rule out CAD in patients with HF.[11] However, it may not be the most appropriate first-line test in individuals with low pre-test probability of CAD. It is debated

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Table 1 Aetiology of heart failure: possible applications of the different imaging techniques (modified from McMurray *et al.*[1])

	Echo	CMR	SPECT	PET	CT
CAD					
Ischaemia	+++	+++	++++	++++	
Hibernation	+++	+++	++++	++++	
Necrosis	++	++++	++	+++	
Anatomy					++++
Valvular					
Stenosis	++++	+			++
Regurgitation	++++	++			
Myocarditis	+	+++			
Sarcoidosis	+	+++		++	
Hypertrophic CMP					
HCM	++++	++++			
Amyloidosis	+++	++++	++	±	
Dilated CMP					
Myocarditis	+	+++			
Eosinophilic syndromes	+	+++			
Iron: haemocromatosis	+	+++			
Iron: thalassemia	+	+++			
Restrictive CMP					
Pericarditis	++	++			+
Amyloidosis	++	+++	++		
Endomyocardial fibrosis	+	+++			
Anderson-Fabry	+	+			
Unclassified CMP					
Takotsubo	++	++	++		
ARVC	++±	+++			

Selection of a test in daily practice should consider availability, local expertise, advantages/disadvantages, and, in the case of several questions to address, which test could best answer several of them.
Grades: ++++, very highly valuable; +++, highly valuable; ++, valuable; +, of interest. CAD, coronary artery disease; CMP, cardiomiopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy.

whether patients with HF and intermediate to high likelihood of CAD should undergo invasive coronary angiography following or preceding non-invasive stress tests. As recommended in European and North-American guidelines,[1] coronary angiography should be performed in patients with angina, whereas in other circumstances, although unproven in clinical studies, a strategy of stress imaging evaluation of ischaemia and viability followed by invasive angiography in patients with evidence of CAD seems the most reasonable approach, since there is no demonstrated benefit of revascularization in patients without ischaemia or viability who might be unnecessarily exposed to the risk of angiography (especially worsening of renal function in patients with reduced glomerular filtration rate).[6]

In some patients, insights in the aetiology of HF can be obtained by examination of the left ventricle under resting conditions (*Table 1*). Regional wall motion abnormalities point to an ischaemic aetiology of HF, whereas typical echocardiographic morphological 7patterns are seen in LV non-compaction (*Figure 3*) or Takotsubo.[12] Similarly, CMR at rest, with late gadolinium enhancement (LGE), may show characteristic aetiological patterns. In non-ischaemic dilated cardiomyopathy, cine images typically show dilated and globally dysfunctional ventricles with LGE in the midwall or subepicardial wall of the left ventricle whereas in ischaemic HF LGE is typically observed in the subendocardium.[13] However, it has been reported that up to 13% of patients with dilated cardiomyopathy and normal coronary arteries show LGE typical of ischaemic LV dysfunction (*Figure 4*). Cardiac magnetic resonance is also well suited to diagnose non-compaction cardiomyopathy given its high spatial resolution and excellent tissue contrast. Other forms of HF may show characteristic patterns on LGE CMR, including sarcoidosis, amyloidosis, Chagas disease, and Fabry's disease and T2* mapping can be used to diagnose myocardial iron overload (*Table 1*).

In most patients with HF and systolic dysfunction, an imaging stress test is recommended to rule out CAD and evaluate the functional significance of coronary stenosis. The choice among different tests

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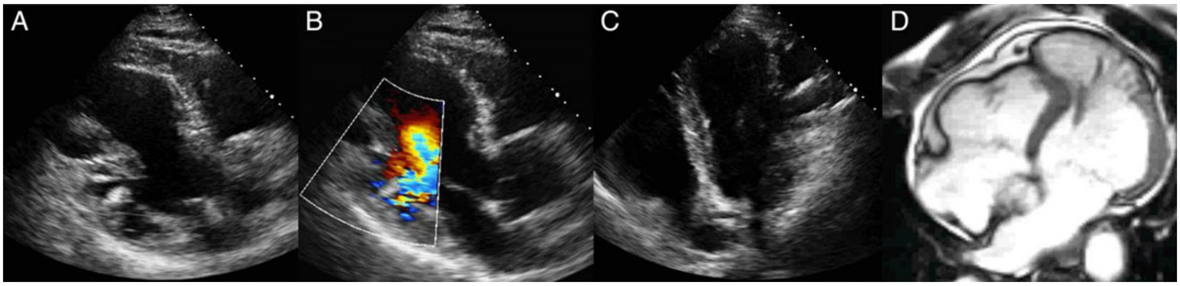

Figure 3 Echocardiographic and cardiac magnetic resonance typical patterns in heart failure due to isolated ventricular non-compaction cardiomyopathy. The echocardiographic parasternal long-axis view without (*A*) and with colour Doppler (*B*) and apical four-chambers view (*C*) show a case of non-ischaemic dilated cardiomyopathy due to isolated ventricular non-compaction. Images show the presence of non-compacted endocardial layer of trabecular meshwork with deep endomyocardial spaces localized on inferior (*A*) and lateral (*C*) walls (maximal end-systolic ratio of non-compacted to compacted layers >2) associated with evidence of deep perfused intertrabecular recesses (*B*). These morphological finding are diagnostic for isolated ventricular non-compaction cardiomyopathy (Jenni criteria[43]). CMR (*D*) confirms the diagnosis.

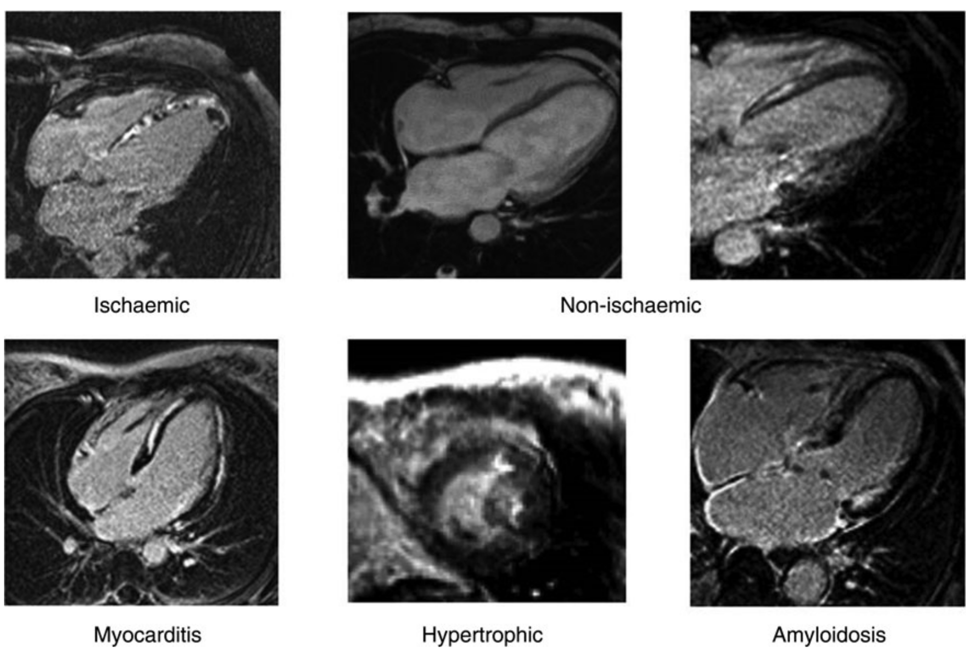

Figure 4 Example of cardiac magnetic resonance late gadolinium enhancement patterns in different aetiologies of heart failure. Ischaemic left ventricular dysfunction typically presents with sub-endocardial or transmural late gadolinium enhancement. Non-ischaemic cardiomyopathy either has no detectable LGE or shows a midseptal stripe pattern. Myocarditis typically shows a midmyocardial or epicardial enhancement in the lateral or anterior and septal walls. Hypertrophic cardiomyopathy shows a wide range of enhancement patterns, including LGE at the septal insertion points. In amyloidosis LGE is typically diffuse and optimal nulling of myocardial signal can be difficult due to the diffuse enhancement.

relies on several factors including patient's characteristics (body size, claustrophobia, presence of non-CMR compatible devices, exercise capacity, etc.), co-morbidities (test using contrast agents should preferably not be used in patients with renal dysfunction), as well as logistic constraints (availability, operator experience). A frequent particular situation is represented by patients with suspected HF and left bundle branch block in whom the accuracy of exercise single photon computed tomography (SPECT) to diagnose CAD is reduced compared with pharmacological SPECT or stress echocardiography,[14] that should be preferred.

Cardiac computed tomography angiography (CCTA) can be used for non-invasive assessment of coronary arteries, using scan protocols, e.g. prospective triggering ultra-high-pitch, very large detectors, advanced reconstruction algorithms, or the step-and-shoot mode that substantially reduce (<2 mSv) radiation exposure.[15] However, CCTA does not assess the functional significance of coronary stenosis that is relevant for patients' management (see below). Therefore, in the CAD rule out workup, CCTA might be considered in patients with equivocal stress imaging results or in those with low intermediate (15% to 50%) pre-test probability of CAD.[9]

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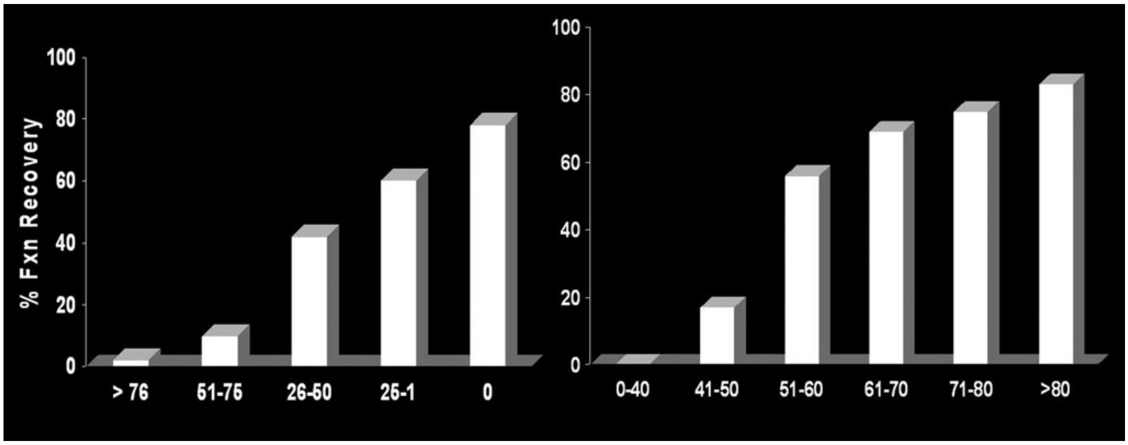

Figure 5 Accuracy for predicting recovery of regional dysfunction in heart failure patients. Assessment of scar using late gadolinium enhancement (left panel) predicts recovery of function with the same relationship reported for nuclear techniques (right panel). The extension of late gadolinium enhancement is expressed as % and reported on *x*-axis in left diagram; the extension of SPECT tracers uptake is expressed as % and reported on *x*-axis in right diagram. The accuracy in predicting recovery of regional dysfunction at rest, indicated as % functional recovery (% Fnx recovery), is quite high in myocardial segments showing very limited LGE extension (lower than 26%) or very preserved SPECT tracers uptake (higher than 60%). Instead, the accuracy for predicting recovery of regional dysfunction at rest become suboptimal for regions showing intermediate extent of LGE similarly to regions showing intermediate uptake of SPECT tracers. Modified from Kim *et al.*[29] (left) and Perrone-Filardi *et al.*[44] (right).

Prognosis and management of heart failure patients based on imaging parameters

The main goal of cardiac imaging is to guide patients' management, ultimately modifying prognosis. Yet, clinicians should recognize that among several imaging parameters that predict outcomes in patients with HF, only few are advocated in guidelines as gate-keepers in the clinical decision-making.

Ejection fraction at rest remains the most powerful prognostic and decision-making parameter in patients with systolic HF. In fact, EF $<$ 35% at rest represents the only imaging parameter recommended in Guidelines for device implantation (ICD, CRT).[16,17]

Quantification and characterization of mitral regurgitation from echocardiographic imaging also drives therapeutic strategy in symptomatic patients. The majority of patients with systolic HF show moderate-to-severe secondary mitral regurgitation due to LV remodelling that substantially affect clinical status and prognosis.[18] Although there is no evidence of an impact on mortality, surgical repair is recommended in patients undergoing bypass cardiac surgery.[19] Percutaneous intervention using MitraClip improves clinical status and reduce valve dysfunction, death, and moderate-to-severe mitral regurgitation at 12 months[20,21] in HF patients, and this procedure represents an alternative to surgery in patients with very high surgical risk.[19] Echocardiography has a key role to identify symptomatic HF patients with mitral regurgitation suitable for MitraClip treatment.[22]

Stress imaging provides key information for management of patients with systolic HF. In patients with low flow–low gradient aortic stenosis and reduced EF (defined by valve area <1 cm^2, EF $<$ 40%, mean gradient $<$40 mmHg), dobutamine stress echocardiography identifies severe aortic stenosis and patients with contractile reserve who show an acceptable operative risk (5%) and more favourable long-term prognosis.[23]

In patients with ischaemic HF, the extent and severity of inducible ischaemia, independently on the imaging modality used, is a key prognostic determinant and identifies patients at high risk in whom revascularization is recommended by Guidelines.[1,9] Although based on retrospective studies, Guidelines recommend revascularization in patients with $>$10% inducible ischaemia in a nuclear imaging stress study [either SPECT or positron emission tomography (PET)] or with $>$3 echocardiographic or CMR ischaemic segments during stress examination.[9] In addition, in patients with ischaemic HF assessment of myocardial viability has been used to recommend revascularization (in patients with evidence of viability and suitable coronary anatomy) or medical therapy (in patients with mostly necrotic myocardium and no inducible ischaemia).[24] Yet, the STICH study[25] reported no impact of viability on the primary endpoint of all-cause mortality in patients with ischaemic severe HF randomized to revascularization or optimal medical therapy. This trial contradicted results of a previous meta-analysis of retrospective studies reporting a substantial benefit of revascularization in ischaemic HF patients with viability.[24] Despite its relevance, the STICH trial presented some limitations[26,27] and current Guidelines[9] recommend revascularization in ischaemic patients with LV viability $>$10%, although the risk-benefit of this approach remains unproven.

In order to assess viability, the recovery of regional contractile function at rest was used as gold standard by all imaging techniques. To this gold standard, nuclear techniques (either SPECT or PET) show greater sensitivity but reduced specificity compared with techniques that assess contractile reserve (echocardiography, CMR). These differences can be more relevant in particular clinical scenarios like patients with dysfunctional myocardium subtended by occluded vessel in whom sensitivity of contractile reserve is suboptimal compared with nuclear techniques.[28]

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Cardiac magnetic resonance evaluation of viability relies on the assessment of transmural distribution of scar using LGE.[29] However, assessment of scar using LGE predicts recovery of function with the same relationship reported for SPECT,[29,30] showing that accuracy is high in myocardial segments with limited fibrosis or preserved SPECT tracers uptake, but becomes suboptimal for regions showing intermediate extent of fibrosis or intermediate uptake of SPECT tracers (*Figure 5*).

Reduced myocardial thickness was also claimed to predict myocardial viability, but up to 18% of dysfunctional myocardial regions with diastolic wall thickness <6 mm show reduced (<50%) scar burden and may improve function and thickness after revascularization.[31]

Yet, implications of myocardial viability are likely more complex than just reflected by recovery of myocardial function at rest. In fact, favourable functional or morphological LV changes may occur after revascularization, without substantial changes in systolic function at rest. Yet, no effects of revascularization other than recovery of contractile function have been adequately explored and this represents a gap in evidence deserving further investigation.

In patients with non-ischaemic systolic HF, CMR LGE predicts all-cause mortality and hospitalization for HF, sudden cardiac death, inducible ventricular arrhythmias, and appropriate ICD shocks,[32] but these prognostic information do not affect management strategies. A relevant potential application of non-invasive imaging in HF patients is the selection of patients for devices (ICD, CRT). Echocardiographic approaches to identify CRT responders looked at the assessment of ventricular asynchrony. However, none of 12 indexes of asynchrony tested in the PROSPECT trial resulted enough accurate for clinical practice.[33] Indeed, in HF patients with narrow QRS but echocardiographic evidence of asynchrony CRT implantation did not influence outcomes.[34] Instead, the CMR approach is based on the assumption that lead implantation is not efficacious in mostly necrotic myocardial areas identified by LGE.[35] However, this approach was never tested in large multicentre studies and is currently not recommended for patient selection for CRT.

Labelling of meta-iodobenzylguanine with radioactive ^{123}iodine (^{123}I-MIBG) depicts the status of cardiac sympathetic innervation.[36] Reduced myocardial ^{123}I-MIBG uptake independently predicts ventricular arrhythmia, sudden cardiac death, and ICD firing in HF patients.[37] Yet, ^{123}I-MIBG has currently no indication in Guidelines[1,17] for selection of patients candidates to ICD. It would be worth to assess in future studies whether ^{123}I-MIBG imaging or other cardiac innervation imaging techniques may identify high-risk patients with mild-to-moderate systolic dysfunction (EF > 35% to normal) currently not candidate to ICD implantation.

Imaging follow-up of heart failure patients

Heart failure patients should be monitored with the goal of identifying sub-clinical haemodynamic deterioration to reduce re-hospitalizations and improve survival. There is no current evidence supporting periodic evaluation of LV function in HF patients who remain stable. However, improvement of EF and reduction of LV systolic and diastolic volumes due to therapy are the only imaging parameters predicting improved prognosis in HF patients.[38] Similarly, reduction of LV volumes of at least 10–15% from pre-implantation values is used to define responders to CRT and predicts improved outcomes.[39] Thus, a reasonable approach would be to re-assess LV function in patients reporting functional deterioration or undergoing CRT implantation. In addition, LV function should be re-assessed periodically in patients undergoing chemotherapy (i.e. after administration of half the total anthracycline cumulative dose and before each subsequent dose).[40]

Perspective: multi-modality imaging in heart failure

Multi-modality imaging represents the combination of anatomical, morphological, and functional parameters from non-invasive imaging techniques. Complementary imaging modalities may be performed separately or in a single-step approach using hybrid systems. Hybrid SPECT-CT or PET-CT enable anatomic and functional evaluation of coronary stenosis[41] whereas hybrid PET/CMR was recently introduced to integrate metabolic, perfusion, structural, and functional parameters.[42]

Although the possibility to obtain complementary information in a single test is appealing, the clinical value and the cost–benefit of these approaches in HF patients remain undetermined and their use must be considered investigational.

Conclusions

Successful application of imaging techniques in HF patients results from integration into clinical care and requires adequate training of cardiovascular specialists. Appropriate utilization of imaging remains the shared responsibility of clinicians who use imaging to assist clinical decision-making and of physicians who perform imaging procedures knowing their strengths and limitations.

Conflict of interest: none declared.

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