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Cardiac Magnetic Resonance: A Multi-Parametric Imaging to Guide Management in Chronic Ischemic Heart Failure

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Chronic heart failure is a major public-health problem with a high prevalence, high mortality and complex treatment. A comprehensive analysis is needed to provide optimal therapy to these patients. Non-invasive imaging plays a central part by offering a complete approach in patients with ischemic heart disease (IHD). Cardiac magnetic resonance imaging (CMR) has emerged as an established advanced multi-parametric imaging modality for the functional and anatomical assessment of cardiovascular disease. This review describes the practical aspects of CMR imaging, and then discusses the role of CMR in the diagnosis and management of chronic IHD, its infarct related complications, such as secondary mitral regurgitation, left ventricular (LV) thrombus, and ventricular tachycardia (VT).

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Introduction

Chronic heart failure has become one of the clinically most important diseases of the heart. The prevalence is high, the treatment is complex, and the mortality is significant. The most detailed report comes from the update of heart disease and stroke statistics from the American Heart Association.[1] A careful and comprehensive analysis is needed to provide optimal (and personalized) therapy to heart failure patients. Most of the information can be provided by non-invasive imaging.

Cardiovascular magnetic resonance (CMR) is an established advanced cross-sectional imaging modality for the functional and anatomical assessment of a wide range of cardiovascular disease. CMR is safe, does not use ionising radiation, provides diagnostic and prognostic information, and guides patient management. One of the key advantages of CMR is its multi-parametric approach, due to the availability of numerous different pulse sequences which can be applied to interrogate different aspects of the cardiovascular system and diagnose its pathological processes.[2] CMR offers a unique multi-parametric assessment, detailing anatomy, function and flow, delineating scar from healthy myocardium, providing accurate tissue characterisation and with the addition

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of stress techniques, can identify inducible myocardial ischaemia. A CMR study typically includes cine imaging in multiple planes for assessment of left ventricular (LV) volumes and global and regional function, stress and rest perfusion for myocardial ischemia and late gadolinium enhancement (LGE) for delineation of scar and assessment of viability. The combination of the above techniques in a single multi-parametric exam allows the quantification of LV ejection fraction, ischemic burden and determines myocardial viability, which can be used to risk-stratify patients and guide revascularisation.[3] See **Table 1**.

Global and regional LV volumetric assessment

Cine cardiac magnetic resonance imaging of parallel, contiguous short-axis slices covering the entire heart over a user-defined number of cardiac phases has become a reference standard by which to assess ventricular function and structure. Global left ventricle and right ventricle volumes and mass are derived from cine CMR without the need for any geometrical assumptions, applying to ventricles of all sizes and shapes, even to those that have experienced extensive remodeling.[5] Cine CMR with steady-state free precession (SSFP)—a relatively recent innovation with high signal-to-noise and tissue-to-blood contrast—enables an accurate identification of even subtle regional wall motion abnormalities.[6] In patients with heart failure, cine CMR demonstrates superiority over other non-invasive techniques, showing less inter-study variability and better reproducibility of the volumetric results. The most common measures quantifiable by cardiac cine CMR are the ventricular dimensions and volumes, myocardial mass, and derived quantities such as ejection fraction, stroke volume, and cardiac output. Additional measures relate to the shape of the ventricle, such as the ratio of the long axis to the short axis, which plays an important part in the pathogenesis of mitral regurgitation. A related measure of left ventricular shape is the sphericity index, defined as the ratio of the major axis to the minor axis of the left ventricle.[7] See **Figure 1**.[4]

Myocardial stress perfusion studies

Basic pathophysiologic principles of coronary blood flow and myocardial perfusion apply also in cardiac magnetic resonance imaging perfusion interpretation. Briefly, in resting conditions, due to the coronary vasodilator reserve, myocardial perfusion is not altered until the coronary artery is 85-90% narrowed. In contrast, during stress the myocardium distal to less severe coronary stenosis (i.e. between 50 to 85%) may become ischemic and the coronary

Table 1. Standard cardiovascular magnetic resonance (CMR) protocol used for assessing ischaemic heart disease (IHD) with their specific clinical utility[4]

IHD assessment CMR protocol sequences	Clinical utility
Static dark blood images of the thorax (HASTE sequence)	Demonstrate anatomy and extra cardiac abnormalities
Bright blood cine images in the following planes 2 Chamber (vertical long axis) 4 Chamber (horizontal long axis) 3 Chamber Short axis (from base to apex of heart) Left ventricular outflow tract (LVOT) Right ventricular outflow tract (RVOT)	Assess global and regional ventricular function. Demonstrate valvular dysfunction Detect ventricular thrombus
Myocardial stress imaging Adenosine stress/rest perfusion or Dobutamine stress wall motion analysis	Myocardial perfusion analysis Myocardial contractile reserve
Post-gadolinium enhancement static images	
Early	Detect ventricular thrombus and microvascular obstruction
Late	Demonstrate myocardial fibrosis
Flow studies in breath hold and free breathing	Valvular functional analysis
Coronary artery imaging	Assess origins and proximal course

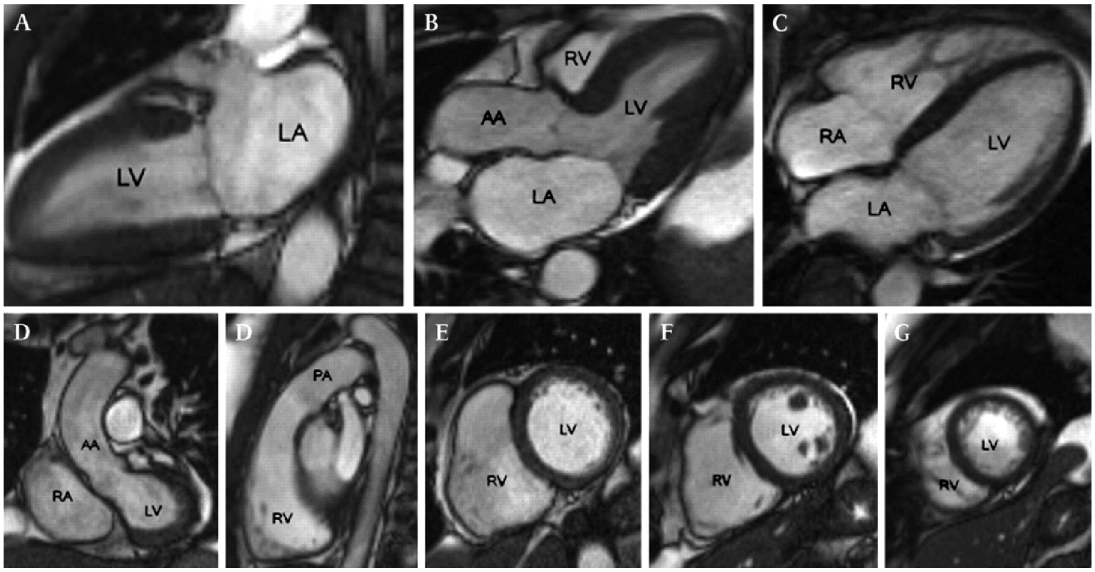

Figure 1. Standard planes of image acquisition on cardiovascular magnetic resonance (CMR) imaging. (A) Two chamber (B) Three chamber (C) Four chamber (D) Left ventricular outflow tract (LVOT) (E) Right ventricular outflow tract (RVOT) (F) Sino-atrial (SA) base (G) SA mid ventricle (F) SA apical ventricle. AA, ascending aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.[4]

artery stenosis can be considered hemodynamically significant. Demonstration of myocardial ischaemia can be performed with either vasodilatory stress agents (adenosine, regadenoson and less commonly dipyridamole or nicorandil) or with an inotropic stress agent (dobutamine). Vasodilatory stress is the preferred method with a bolus of Gadolinium (Gd)-based contrast agents (GBCA) delivered at peak stress. On first pass perfusion CMR, relative hypoperfusion indicating ischaemia is detected by reduced/delayed peak signal intensity during the myocardial contrast passage. Inotropic stress is mostly used to detect wall motion abnormalities in the presence of functionally significant coronary stenosis without the need for a GBCA although first pass perfusion imaging at peak inotropic stress may also be performed for additional value.[8] Low-dose dobutamine stress CMR (5-10 mcg/kg/min) relies on the demonstration of inotropic reserve in post-ischaemic viable myocardium. Cine imaging is performed at each stage of inotropic stress to assess all segments of the left ventricular myocardium in order to determine wall thickness and contractility. A 2mm, or more, increase in systolic wall thickness during inotropic stress infers myocardial viability.[9] At present this technique has been well validated, showing similar or better accuracies when compared to routinely used techniques such SPECT imaging[10] In a meta-analysis by Nandalur et al. including 24 studies (1516 patients, high disease prevalence), perfusion imaging demonstrated a sensitivity of 91% and a specificity of 81%.[11] Compared to stress echocardiography, MRI provides reliable image quality not limited by the adequacy of the acoustic window. Per stress level, images can be easily acquired in standardized (repeatable) planes, and easily compared on an off-line workstation reducing operator-dependency. Patients with poor acoustic windows benefit the most from CMR stress testing. See **Figure 2**.[4]

Late gadolinium enhancement for scar detection and viability assessment

Gadolinium contrast used with CMR remains confined to the extracellular space in normal myocardium. Within infarcted myocardium, the volume of distribution for gadolinium contrast is significantly expanded, reaching 60–70% in scar tissue. As early as 3-4 min after administration of gadolinium contrast, the expanded distribution volume can be reliably detected with CMR to demarcate non viable myocardium,[12] with at least 4–6-fold greater spatial

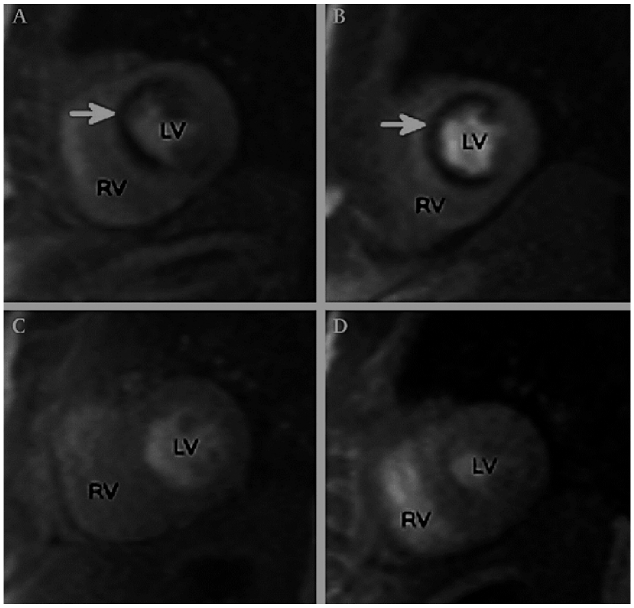

Figure 2. Short Axis LV mid (A, C) and apical cavity (B, D) views in peak stress (A, B) and rest (C, D). Note significant subendocardial stress induced perfusion defect (arrow) in the antero septal wall which completely resolves at rest. LV, left ventricle; RV, right ventricle.[4]

resolution and a greater contrast-to-noise ratio than can be achieved with nuclear scintigraphy. The focal signal hyperintensity of infarcted myocardium, or myocardial scar tissue, is highlighted by suppressing the signal from normal myocardium.[13] Late gadolinium enhancement (LGE) images delineate the transmural extent of infarction (**Figure 3**),[14] thereby distinguishing between reversible and irreversible myocardial injury, regardless of the extent of wall motion at rest, the age of the infarct, or the reperfusion status.[15]

Late Gadolinium Enhancement (LGE) imaging is consistently more sensitive and specific than any other techniques in detecting and sizing the spatial extent of myocardial infarction.[15] The transmural extent of LGE can predict the response of left ventricular function to b-blocker therapy in patients with heart failure.[16] Orn et al.[17] found that scar size assessed by CMR was the strongest independent predictor of ejection fraction and left ventricular volumes in acute myocardial infarction, and of patients with heart failure. The transmural extent of hyper-enhancement predicts functional improvement after revascularisation.[18] Segments with <25% of transmural hyper-enhancement are likely to exhibit functional recovery, whilst those segments with >75% transmurality are unlikely to benefit from revascularisation, irrespective of the extent of the resting wall motion abnormality.[19] Furthermore transmurality of LGE is a stronger predictor of regional and global functional recovery following revascularization than resting end diastolic wall thickness.[20] The assessment of myocardial viability using a 50% transmural cut off on LGE imaging has been reported to have a sensitivity of 95% (95% CI: 93-97%) and specificity of 51% (40-62%) to predict segmental functional recovery following revascularisation. Inotropic reserve assessed by low dose dobutamine has significantly higher specificity (91%) suggesting a combination of the two techniques might improve diagnostic performance for those segments with 25-75% of transmural LGE.[21] It was shown recently that CMR measurements of gadolinium distribution volumes in viable myocardium provide a novel marker of extracellular remodeling and diffuse fibrosis in patients with heart failure and dilated cardiomyopathy,[22] pointing to the versatility of CMR for extensive tissue characterization in patients with heart failure.

Infarct-related complications

CMR can also assess complications after myocardial infarction, such as left ventricular mural thrombus, aneurysmal dilatation, and papillary muscle involvement causing mitral regurgitation and rupture of the interventricular septum.[23] Ventricular thrombi are easily missed on transthoracic echocardiography especially when located in the LV apex or when trapped within the endocardial trabeculations. Thrombus is an avascular structure, on LGE images it usually appears as a mass with low signal intensity surrounded by areas of high signal intensity such as cavity blood (**Figure 4**).[24]

Secondary mitral regurgitation occurs frequently in patients with ischemic heart failure, and is characterized by a combination of reduced LV closing forces (due to LV dysfunction or dyssynchrony) and global and regional LV remodeling which leads to distortion of the subvalvular apparatus of the mitral valve, displacement of the papillary muscles, tethering of the mitral leaflets, and failure of mitral valve coaptation. Secondary mitral regurgitation results in LV volume overload, which further worsens LV remodeling and mitral valve incompetence. The presence of significant secondary mitral regurgitation provides incremen-

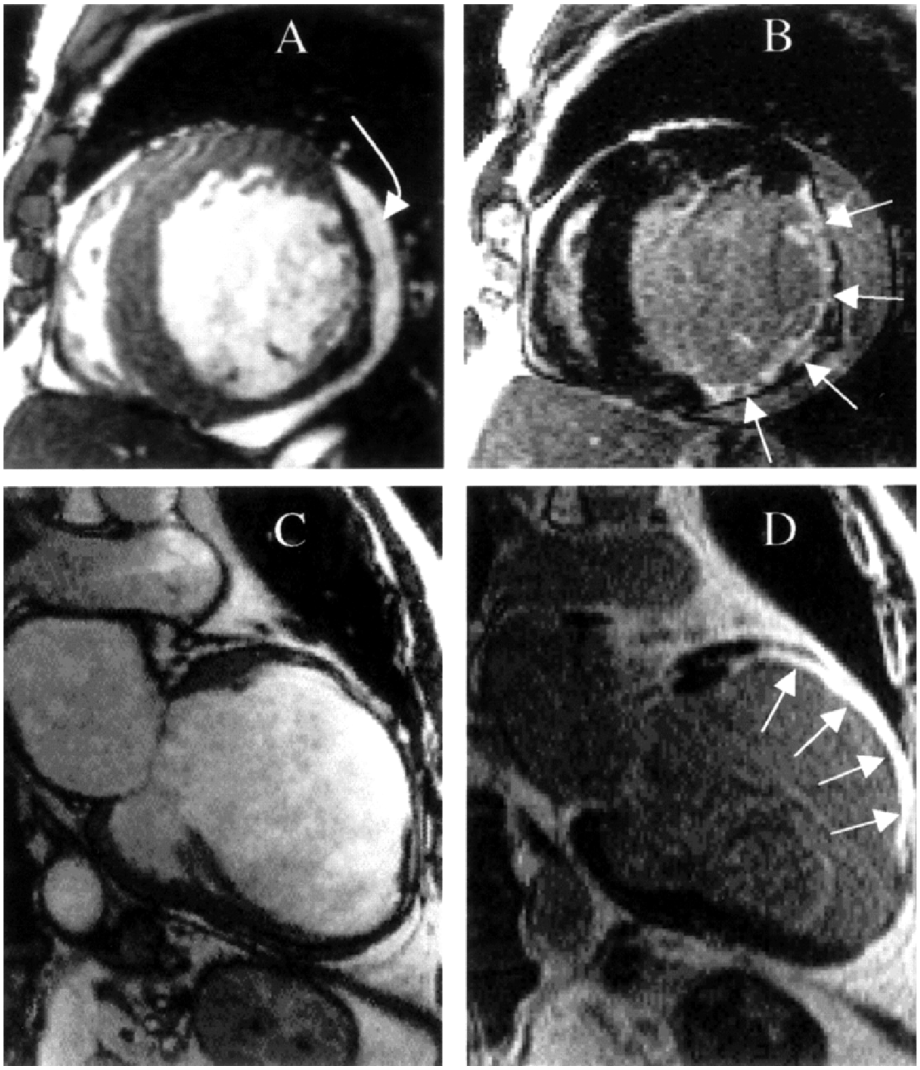

Figure 3. This figure shows two different patients, with the top row showing a lateral infarction, and the bottom row showing an anterior infarction. The left column (A and C) shows single frames from gradient echo cines, and the right column (B and D) shows the gadolinium enhanced images. The bright areas in B and D are infarcted tissue which is brightly enhanced (straight arrows). The infarct in the short axis plane (B) extends from the inferior wall to the anterolateral wall, and is mainly non-transmural. In particular, at 4 o'clock a significant rim of viable epicardial tissue is present and wall thickness is preserved. However, wall thinning has occurred elsewhere where the transmural extent of infarction is greater. The infarct in the anterior wall of the vertical long axis plane (D) is transmural, however, and considerably greater thinning and ventricular remodeling has taken place. This technique allows transmural high resolution infarct depiction in-vivo for the first time. The curved arrow shows a pericardial effusion. Reproduced from Rajappan et al., Eur J Heart Failure. 2000;2:241–52.[14]

tal prognostic information over LVEF. Significant secondary mitral regurgitation was associated with increased risk of heart failure hospitalization and all cause mortality.[25] Therefore, accurate quantification of secondary mitral regurgitation severity is crucial for clinical decision making in heart failure patients. Two

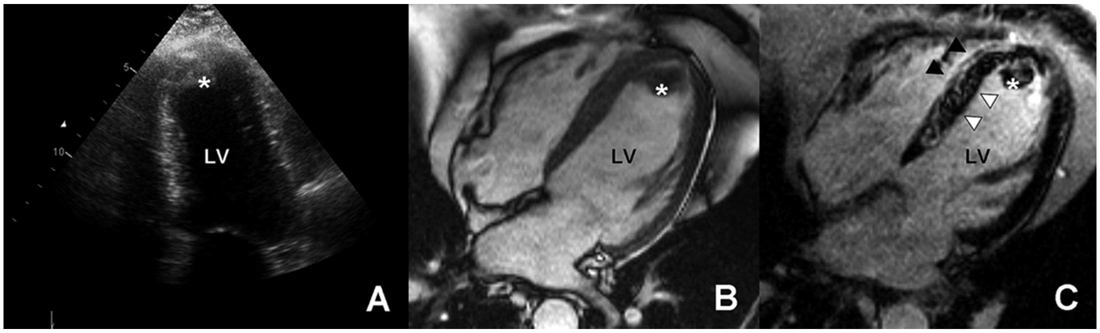

Figure 4. Left ventricular (LV) thrombus formation on delayed gadolinium contrast cardiac MRI and transthoracic echocardiography. Transthoracic echocardiographic appearance of a thrombus (asterisk) in the apex of the left ventricle (A); cine cardiovascular magnetic resonance of the same patient also delineates the apical thrombus (B); late gadolinium enhancement imaging clearly confirms the avascular non-enhancing thrombus (asterisk, dark) close to the transmural infarcted myocardium (bright hyperenhanced, black arrowheads) with areas of microvascular obstruction (black, white arrowheads) (C). Courtesy of Dr A C van Rossum, Dr R Nijveldt, Department of Cardiology, VU University Medical Center, Amsterdam, the Netherlands, and Dr B J Bouma, Department of Cardiology, Academic Medical Center, Amsterdam, the Netherlands.

dimensional echocardiography remains the mainstay imaging technique to assess the severity and mechanism of secondary mitral regurgitation.[26]

The suitability for surgical restrictive mitral valve annulopasty is influenced by several geometrical aspects of the mitral valve and left ventricle, and also by the presence of extensive myocardial scar, which has been associated with increased mortality rates after surgical repair.[27]

Furthermore CMR is able to detect, accurately size and assess the haemodynamic significance of a post-infarct ventricular septal defect (VSD), potentially guiding the suitability and sizing for a percutaneous VSD closure device.[28] Accurate volumetric quantification of both the right and left ventricles, or comparison of flow measurements of the pulmonary and systemic circulations, can also be used to calculate the shunt ratio. CMR is also useful in the detection of ventricular aneurysm, pseudoaneurysms and assessment and quantification of mitral regurgitation post AMI. Furthermore, the high spatial resolution of CMR allows the detection and quantitation of RV infarction with LGE and cine imaging, which has additional prognostic importance.[29]

Patients with ischemic heart failure and depressed LVEF (<35%) have an increased risk of arrhythmic death.[30] Left ventricular volumes and LVEF are important parameters for the risk stratification and management (particularly device therapy) of heart failure patients. CMR techniques can capture and characterize the multifaceted process of infarct remodeling, and shed light on novel markers beyond infarct and scar size, cavity enlargement, and left ventricular function. The border zone of infarction with intermediate signal intensity on LGE images provides a stronger association with electrophysiological substrates of ventricular arrhythmias than with left ventricular ejection fraction. The border zone was strongly associated with post myocardial infarction mortality in a small group of patients post myocardial infarction.[31] See **Figure 5**.[32]

Various trials have demonstrated the prophylactic benefit of an ICD in these patients. However, the percentage of patients that require ICD therapy (appropriate shocks) to prevent ventricular tachycardia/fibrillation (VT/VF) at follow-up is relatively low, suggesting that a substantial percentage of patients may not benefit from ICD.[33] Currently, the LVEF (±30-35%) used as the main selection criterium for ICD therapy.[34] The precise substrate for VT/VF however is unknown, but may be related to scar tissue (infarct zone) and the heterogenous border zone around the infarct core (mixture of viable myocardium interspersed with fibrous and scar tissue). Non-invasive imaging may eventually help in patient selection for ICD implantation. The presence, extent, and characteristics of myocardial scar assessed with contrast-enhanced MRI have incremental prognostic value over LVEF to

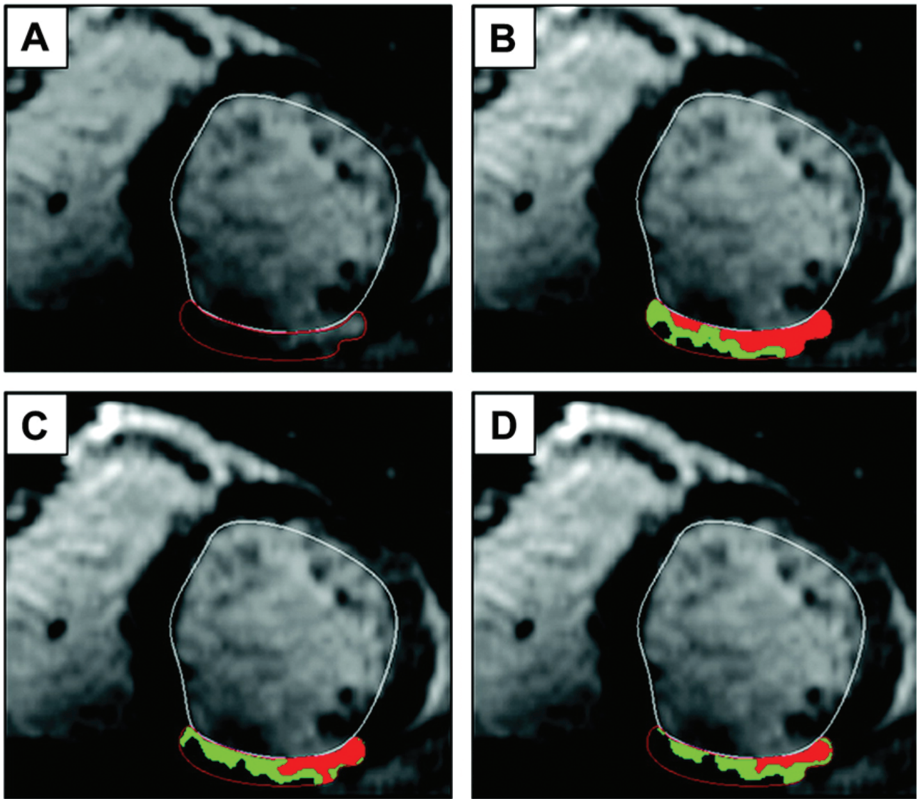

Figure 5. Algorithms applied to a contrast-enhanced cardiac magnetic resonance (CE-CMR) image. (A) Manual segmentation applied to a CE-CMR image, both left ventricle endocardium and scar—white and red areas, respectively. (B), (C), (D) Same images postprocessed by an algorithm using 50%, 60%, and 70% of maximum signal intensity, respectively.[32]

predict the occurrence of VT/VF.[35] Subsequent studies quantifying the extent of contrast-enhanced tissue (scar mass) revealed that the arrhythmic risk increased significantly when the scar mass exceeded 1.4-5% of the LV volume.[36]

Conclusion

Patients with chronic heart failure need a careful and stepwise diagnostic analysis. Cardiac magnetic resonance imaging allows comprehensive and accurate assessment of patients chronic ischemic heart failure and it is the current gold standard imaging modality for assessment of ventricular function. The complete information provided from CMR, both anatomical and functional assessment, can guides physician to understand more about the pathophysiological process of ischemic heart disease, and a better management in the intervention of chronic heart failure and its related complications.

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