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# Magnetic resonance imaging and multi-detector computed tomography assessment of extracellular compartment in ischemic and non-ischemic myocardial pathologies

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## Abstract

Myocardial pathologies are major causes of morbidity and mortality worldwide. Early detection of loss of cellular integrity and expansion in extracellular volume (ECV) in myocardium is critical to initiate effective treatment. The three compartments in healthy myocardium are: intravascular (approximately 10% of tissue volume), interstitium (approximately 15%) and intracellular (approximately 75%). Myocardial cells, fibroblasts and vascular endothelial/smooth muscle cells represent intracellular compartment and the main proteins in the interstitium are types I / III collagens. Microscopic studies have shown that expansion of ECV is an important feature of diffuse physiologic fibrosis (*e.g.*, aging and obesity) and pathologic fibrosis [heart failure, aortic valve disease, hypertrophic cardiomyopathy, myocarditis, dilated cardiomyopathy, amyloidosis, congenital heart disease, aortic stenosis, restrictive cardiomyopathy (hypereosinophilic and idiopathic types), arrhyth-

mogenic right ventricular dysplasia and hypertension]. This review addresses recent advances in measuring of ECV in ischemic and non-ischemic myocardial pathologies. Magnetic resonance imaging (MRI) has the ability to characterize tissue proton relaxation times (T1, T2, and T2\*). Proton relaxation times reflect the physical and chemical environments of water protons in myocardium. Delayed contrast enhanced-MRI (DE-MRI) and multi-detector computed tomography (DE-MDCT) demonstrated hyper-enhanced infarct, hypo-enhanced microvascular obstruction zone and moderately enhanced peri-infarct zone, but are limited for visualizing diffuse fibrosis and patchy microinfarct despite the increase in ECV. ECV can be measured on equilibrium contrast enhanced MRI/MDCT and MRI longitudinal relaxation time mapping. Equilibrium contrast enhanced MRI/MDCT and MRI T1 mapping is currently used, but at a lower scale, as an alternative to invasive sub-endomyocardial biopsies to eliminate the need for anesthesia, coronary catheterization and possibility of tissue sampling error. Similar to delayed contrast enhancement, equilibrium contrast enhanced MRI/MDCT and T1 mapping is completely noninvasive and may play a specialized role in diagnosis of subclinical and other myocardial pathologies. DE-MRI and when T1-mapping demonstrated sub-epicardium, sub-endocardial and patchy mid-myocardial enhancement in myocarditis, Behcet's disease and sarcoidosis, respectively. Furthermore, recent studies showed that the combined technique of cine, T2-weighted and DE-MRI technique has high diagnostic accuracy for detecting myocarditis. When the tomographic techniques are coupled with myocardial perfusion and left ventricular function they can provide valuable information on the progression of myocardial pathologies and effectiveness of new therapies.

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**Key words:** Myocardial viability; Ischemic/non-ischemic

heart diseases; Magnetic resonance imaging; Multi-detector computed tomography; Cellular compartments; Contrast media

**Core tip:** This review addresses recent advances of measuring of extracellular volume (ECV) in ischemic and non-ischemic myocardial pathologies. The main approaches that are used for probing ECV are equilibrium contrast enhanced magnetic resonance imaging/multi-detector computed tomography and magnetic resonance imaging (MRI) longitudinal relaxation time mapping. These noninvasive techniques are currently used, but at a lower scale, as alternative to invasive endomyocardial biopsies to eliminate anesthesia, coronary catheterization and tissue sampling error. ECV measurements may aid in early detection of various myocardial pathologies. Delayed contrast enhanced-MRI (DE-MRI) and when T1-mapping demonstrated sub-epicardium, sub-endocardial and patchy mid-myocardial enhancement in myocarditis, Behcet's disease and sarcoidosis, respectively. Furthermore, recent studies showed that the combined technique of cine, T2-weighted and DE-MRI technique has high diagnostic accuracy for detecting myocarditis. When the tomographic techniques are coupled with myocardial perfusion and left ventricular function it can provide valuable information on the progression of myocardial pathologies and effectiveness of new therapies.

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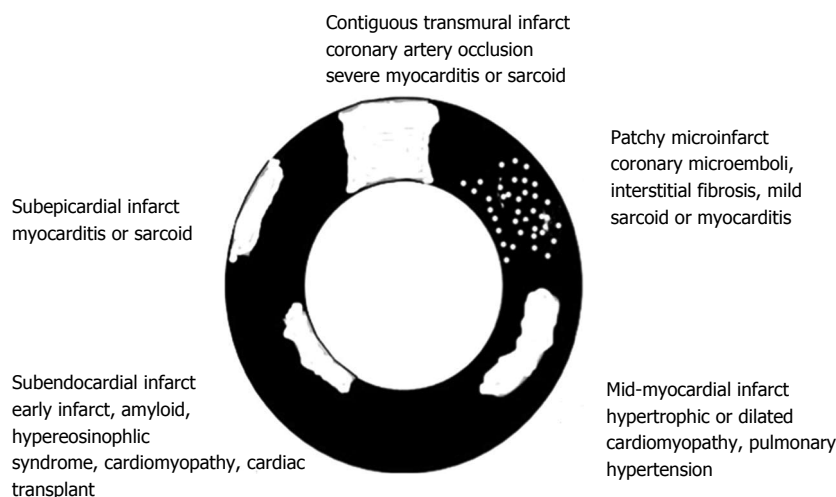
## INTRODUCTION

Ischemic and non-ischemic cardiomyopathies have become a worldwide epidemic of the 21<sup>st</sup> century with increasing impact on healthcare systems. The 2012 European Society of Cardiology and 2013 American College of Cardiology Foundation/American Heart Association guidelines have set the stage for current therapy to reduce mortality and morbidity<sup>[1,2]</sup>. Revascularization of coronary arteries in acute myocardial infarct (AMI) have become the treatment of choice and revascularization procedures have evolved significantly. Because X-ray coronary angiography-the clinically accepted reference standard for demonstrating coronary artery disease is invasive and provides information only on the anatomical status of coronary obstructive lesions several noninvasive methods have been developed to aid in the assessment of the functional status of myocardium, namely contraction and perfusion as well as microvascular and cellular integrity, including positron emission tomography and contrast-enhanced echocardiography. More recently, delayed contrast-enhanced (DE) magnetic resonance

imaging (MRI)<sup>[3-13]</sup>. Extracellular MR contrast media identifies hyperenhanced infarct, hypoenhanced microvascular obstruction zone and a moderately enhanced peri-infarct zone in acute myocardial infarction<sup>[5,6]</sup>. Delayed contrast enhanced-MRI (DE-MRI) has sensitivity of 99% for measuring AMI/scar infarct extent and 94% for measuring the transmural enhancement<sup>[3,7,8]</sup>. Transmural enhancement was used to predict recovery of regional function in enhanced segments<sup>[9]</sup>. A cutoff of 50% transmural enhancement was the threshold of recovery of regional function after intervention, where < 50% transmural enhancement predicted recovery in 53% of segments, while > 50% transmural enhancement was associated with negligible recovery (8% of segments)<sup>[10]</sup>. Furthermore, < 25% transmural enhancement predicted residual viability in 82% of segments. DE-MRI has been clinically used to diagnose and specify different types of ischemic and non-ischemic cardiomyopathies based on the pattern and location of enhancement.

In ischemic cardiomyopathy the sub-endocardium is always enhanced on DE-MRI<sup>[3,7,8]</sup>, while in dilated cardiomyopathy, a patchy mid-myocardial pattern of enhancement is seen<sup>[12]</sup>. Patients with mid-myocardial enhancement are at higher risk of sudden cardiac death and arrhythmias<sup>[13]</sup>. Furthermore, patients with restrictive cardiomyopathy showed delayed myocardial enhancement over the entire sub-endocardial circumference<sup>[14]</sup>. DE-MRI and T1-mapping demonstrated sub-epicardial, sub-endocardial and patchy mid-myocardial enhancement in myocarditis specific cardiomyopathies such as Behcet's disease and sarcoidosis, respectively. In Behcet's disease, enhancement of sub-endocardial fibrosis in the right ventricle is considered a feature of the disease. Vignaux<sup>[15]</sup> observed delayed enhancement in sarcoidosis patients in specific locations [basal interventricular septum, lateral left ventricular (LV) wall] and distribution patterns (patchy or striate that do not involve the sub-endocardium) and in advanced cases of diffuse and focal pathologies. In non-ischemic dilated cardiomyopathy, Assomull *et al*<sup>[13]</sup> showed that the presence of delayed myocardial enhancement was associated with a 3-fold increase of hospitalization for heart failure or cardiac death and a 5-fold increase of sudden cardiac death or ventricular arrhythmias. In hypertrophic cardiomyopathy, the extent of differentially enhanced myocardium assessed on DE-MRI was linked with progressive disease and markers of clinical risk for sudden death<sup>[16]</sup>.

Other MRI studies showed discordant results about the relationship between infarct enhancement and regional LV function. Beek *et al*<sup>[17]</sup> reported that 25% of LV segments with transmural enhancement showed potential improvement in function at 13 wk. In another recent study, Dall'Armellina *et al*<sup>[18]</sup> found that AMI does not necessarily equate with irreversible injury and severely underestimate salvaged myocardium on DE-MRI. Accordingly, new strategies have been developed to quantify diffuse myocardial fibrosis and small infarcted areas using equilibrium contrast enhanced magnetic resonance imaging/multi-detector computed tomography (MRI/MDCT)



**Figure 1 Schematic presentation of various types (patchy and contiguous) and locations (epicardium, midmyocardium and endocardium) of myocardial infarct in different cardiac diseases.** In acute myocardial infarct > 30% of the patients have a hypoenhanced microvascular zone in the core of contiguous infarct. Reactive interstitial fibrosis is seen in hypertension, valvular, diabetic and genetic diseases as well as aging, while infiltrative interstitial fibrosis is evident in amyloidosis and Anderson-Fabry disease. The replacement of myocardium with scar tissue is seen in inflammatory disease, chronic ischemia/coronary occlusion (contiguous), chronic renal insufficiency (patchy) and genetic and toxic diseases.

and T1-mapping techniques<sup>[19-27]</sup>. Lee *et al.*<sup>[28]</sup> found that the extracellular volume (ECV) in healthy volunteers is stable between 8.5-23.5 min after gadolinium-based contrast media administration and in infarcted myocardium between 12-50 min<sup>[29]</sup>. These methods overcome the question of the relationship between myocardial enhancement, function and diffuse fibrosis on delayed enhancement. They also allowed for the detection of greater collagen content in the extracellular compartment of myocardium in aging, failing heart, congenital heart, infiltrative heart, hypertension and hypertrophic cardiomyopathy pathologies than normal myocardium<sup>[19,30-34]</sup>.

Visualization of small infarcted areas, peri-infarct zone, patchy microinfarct and diffuse fibrosis remains difficult using existing DE-MRI and DE-MDCT because of low sensitivity, minor/vague alterations in tissue structure, nonspecific enhancement or overlapping with other confounding diseases. On the other hand, experimental studies have shown expansion of ECV in conditions where myocardial damage is invisible on MRI<sup>[26,27]</sup>. A clinical MRI study found that the ECV of AMI is higher than the ECV in non-ischemic cardiomyopathies, suggesting that the damage is greater damage in the former. The study also showed that the location and pattern of enhancement differs between non-ischemic and ischemic cardiomyopathies<sup>[35]</sup> (Figure 1).

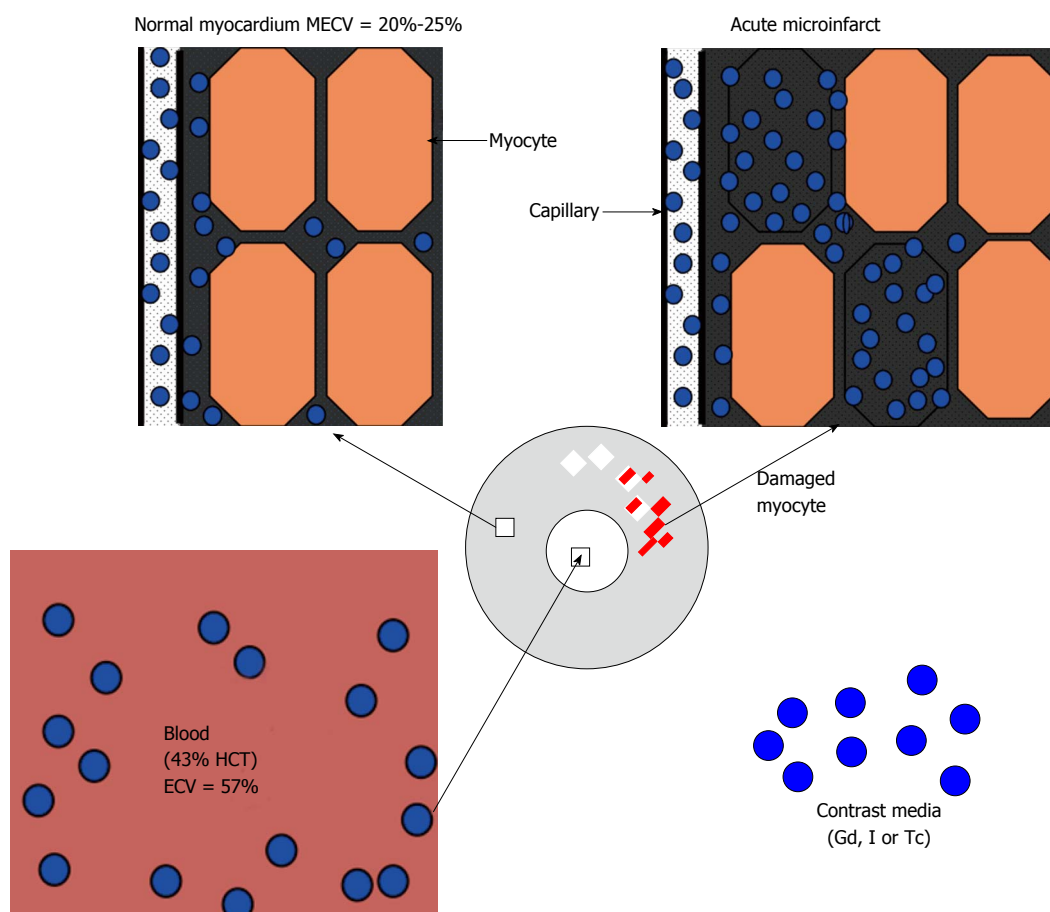
## MYOCARDIAL COMPARTMENTS

Microscopic studies revealed three fluid compartments in healthy myocardium, namely intravascular (approximately 10% of tissue volume), interstitial (approximately 15%) and intracellular (approximately 75%) compartment (Figure 2). It should be noted that the terms extracellular volume (ECV), volume of distribution, fibrosis index, and volume fraction of extravascular extracellular matrix share the same parameters for measuring the ECV by ad-

justing the contrast media partition coefficient with blood hematocrit<sup>[26,27,36]</sup>.

Intracellular water accounts for 79% of total water or about 380 mL/100 g of dry tissue and varies between individuals and species<sup>[37]</sup>. The intracellular compartment includes myocardial cells, fibroblasts and vascular endothelial/smooth muscle cells. The main constituent proteins of the interstitial compartment are types I and III collagens. Water permeable membranes separate these compartments. Blood plasma and interstitial fluid exchange through pores and intercellular clefts in capillary endothelium.

The fluid in the interstitial compartment consists of a water solvent containing sugars, salts, fatty acids, amino acids, coenzymes, hormones, neurotransmitters and cellular waste products. The exchange of fluid and accompanying solutes between compartments is governed by hydrostatic and oncotic forces. These forces are typically balanced to maintain a constant fluid volume in the compartments. The molecular pathways that contribute to extracellular compartment remodeling post-MI, however, are multifactorial and related to; (1) the increase in osmotic colloidal pressure resulting from the leakage of plasma proteins<sup>[38]</sup>; (2) the degradation of the extracellular matrix<sup>[39]</sup>; and (3) heterogeneous or homogeneous loss of membrane integrity of myocardial cells. Disturbance in microvascular permeability causes extravasation of plasma macromolecules that subsequently leads to water imbalance and interstitial edema. Loss of the membrane integrity of myocardial cells further expands the extracellular compartment; and that is the basis for assessing viability and fibrosis (Figure 2). Expansion of ECV in ischemic and non-ischemic heart diseases is strongly associated with adverse outcomes<sup>[40]</sup>. Expansion of ECV has been seen in myocarditis, hypertrophy, dilated cardiomyopathy, amyloidosis, congenital heart disease, aortic stenosis, restrictive cardiomyopathy, arrhythmogenic right



**Figure 2** The three fluid compartments in healthy myocardium, namely intravascular (approximately 10% of tissue volume), interstitial (approximately 15%) and intracellular (approximately 75%) compartments. ECV: Extracellular volume; HCT: Hematocrit; Gd: Gadolinium; I: Iodine; Tc: Technetium; MECV: Myocardial extracellular volume.

ventricular dysplasia, hypertension and myocardial infarction (Figure 3).

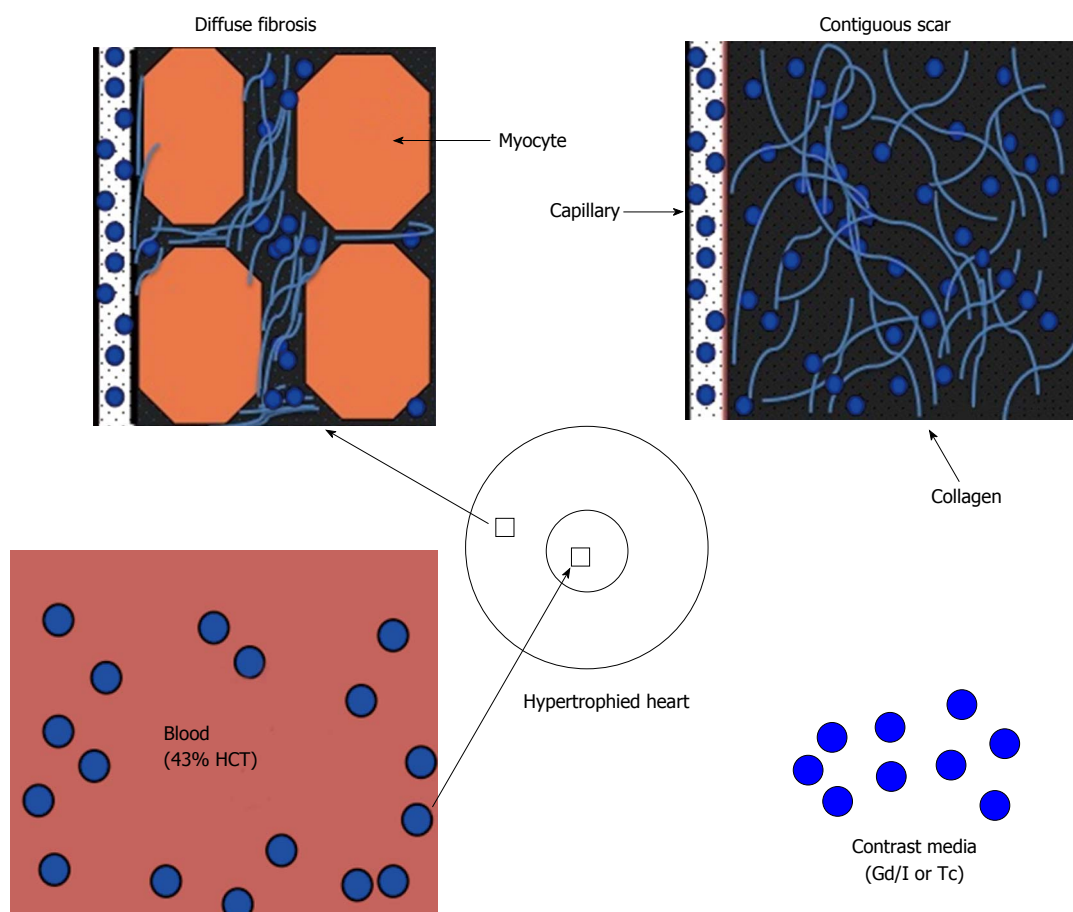
Proton relaxation times ( $T_1$ ,  $T_2$ , and  $T_2^*$ ) reflect the composition of water protons in tissues. In 1992 several studies showed relationship between  $T_1$  change and extracellular MR contrast media content in myocardium<sup>[41-43]</sup>. Extracellular contrast media are rapidly distributed throughout the extracellular compartment in most tissues, but not in the brain, testis and retina. They are rapidly cleared from the circulation *via* the kidney. The quantity of contrast media distributed into a particular tissue is a function of physical extent of extracellular space and physiologic processes (blood flow, volume and diffusion) that distribute the agent into and remove it from the tissue. In myocardial infarct, investigators observed progressive alterations in structure and composition of the extracellular compartment<sup>[44,45]</sup>. Interstitial edema in infarcted myocardium causes increase in longitudinal ( $T_1$ ), transverse ( $T_2$ ) and  $T_2^*$  relaxation times<sup>[46]</sup> and administration of contrast media causes shortening<sup>[19,30-32]</sup>. The decrease in the  $T_1$  relaxation time is greater in infarcted than healthy myocardium, resulting in differential enhancement.  $T_1$  assessment has also been used to measure macromolecular content, water binding and water content in tissues. The  $T_1$  relaxation time is defined as the time when longitudinal proton magnetization

recovers approximately 63% of its equilibrium value.  $T_2^*$  relaxation time refers to decay of transverse magnetization caused by a combination of spin-spin relaxation and magnetic field inhomogeneity. The differential attenuation of infarct and viable myocardium on MDCT relies on X-ray absorption by iodine.

## STRATEGIES FOR ESTIMATION OF ECV

The gold standard method for estimation of ECV in patients has been sub-endocardial biopsy. This method, however, has relatively high inherent risk, is limited to small regions and is prone to sampling site error<sup>[47,48]</sup>. Visualization of large AMI and scar infarct on MRI and MDCT relies on the differences in signal intensity/attenuation between damaged and remote undamaged tissue to generate image contrast. It has been reported that undetected infarct account for at least 20% of all clinical cases of AMI and carry a prognosis as poor as detected ones<sup>[49]</sup>. Furthermore, signal intensity on DE-MRI is displayed on an arbitrary scale and tissue signals or contrast media concentration cannot be quantified. Patchy microinfarct and diffuse fibrosis in non-ischemic myocardial cardiomyopathies necessitate alternative techniques beyond current DE-MRI or DE-MDCT. Fast MRI and MDCT image acquisition,  $T_1$  sensitive sequences and





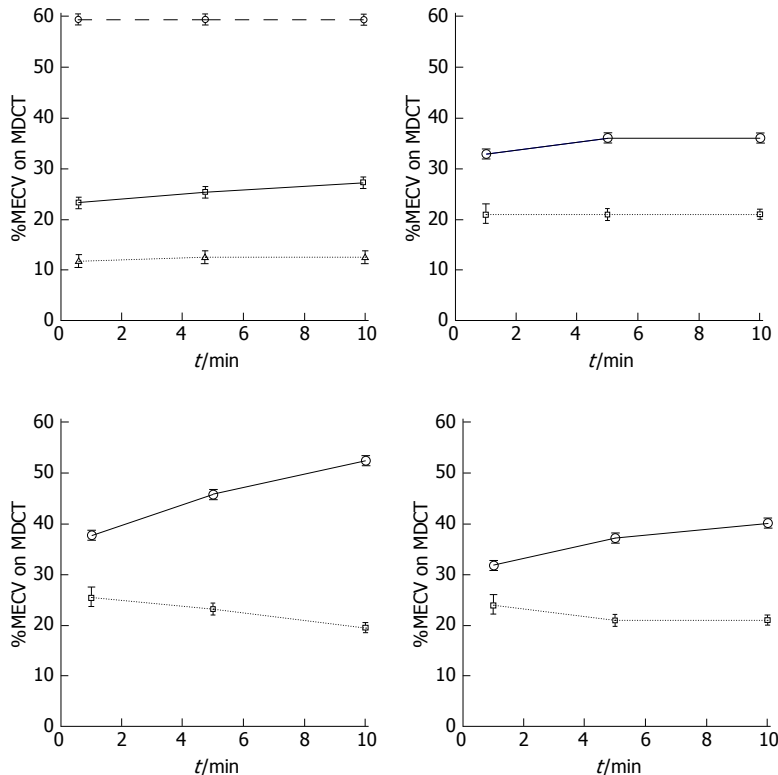
**Figure 3** Schematic presentation of diffuse myocardial fibrosis in non-ischemic heart diseases (left) and contiguous chronic infarct (right) in ischemic heart disease. HCT: Hematocrit; Gd: Gadolinium; I: Iodine; Tc: Technetium.

contrast media allow the measurement of ECV. Look-Locker and echo planar MRI sequences as well as MDCT were used for non-invasive estimation of ECV. More recently, investigators have used MRI for T1 mapping and measuring ECV. The differences in regional T1 can be visualized as a grey-scale or color map<sup>[50-53]</sup>. Investigators also found that equilibrium contrast and T1 mapping methods provide information, beyond what is visually evident on DE-MRI/DE-MDCT<sup>[48,50]</sup>. These methods rely on three principles: (1) the measurement of global myocardial and blood T1 relaxation time/signal attenuation before contrast media administration; (2) a second measurement of T1 relaxation time/signal attenuation during contrast media equilibrium phase; and (3) a direct measurement of the blood contrast media volume of distribution. Extracellular inert gadolinium-based MR and iodinated computed tomography (CT) contrast media are crucial because they diffuse passively and rapidly between intravascular and extracellular compartments (Figure 4). Investigators have used longitudinal relaxation rate (1/longitudinal MR relaxation time; 1/T1) on MRI and myocardial signal attenuation on CT to quantify regional ECV<sup>[22,41-43,54]</sup>. The calculation of ECV is based on the ratio of the difference in signal attenuation or 1/T1 before and after administration of contrast medium in myocardium divided by the difference in signal attenu-

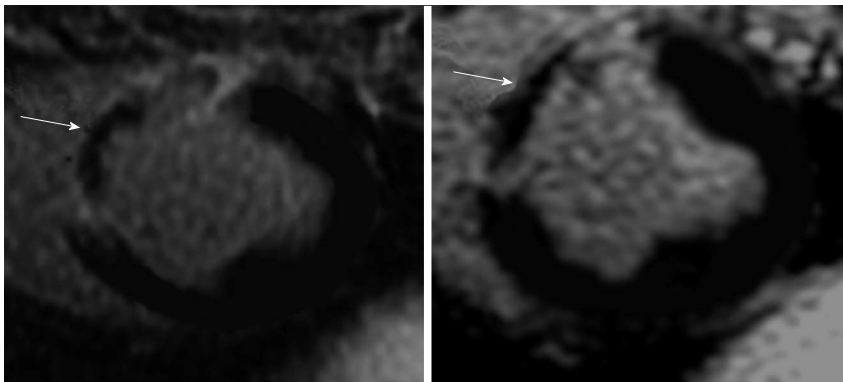
ation or 1/T1 the blood pool. The increase in regional signal intensity on MRI and a decrease in attenuation on CT are attributed to the increase in ECV. Enhancement is expressed in Hounsfield or arbitrary units and employs tissue with lowest signal intensity as a reference for normality. The reason for using 1/T1 and not signal intensity on MRI is that signal intensity is not linearly correlated with contrast concentration. Unlike MR contrast media, signal attenuation after administration of CT contrast media is linearly correlated with contrast media concentration.

Our group was the first to find on MRI that the expansion in ECV is the mechanism for differential enhancement of infarct from healthy myocardium. We also demonstrated the peri-infarct zone<sup>[26,27,55]</sup>. Later, Klein *et al*<sup>[56]</sup> confirmed in patients with AMI that the partition coefficient is elevated in infarct compared to remote myocardium. Lee *et al*<sup>[28]</sup> found in healthy volunteers that the ECV is  $27\% \pm 1\%$  while Broberg *et al*<sup>[33]</sup> found it is slightly lower ( $22\% \pm 2\%$ ). Schelbert *et al*<sup>[29]</sup> claimed that similar ECV values can be obtained by bolus ( $21\% \pm 2\%$ ) and infusion ( $25\% \pm 2\%$ ) approaches.

Recent studies have also shown that MDCT allows for assessment of myocardial viability and visualization of coronary stenosis<sup>[57-59]</sup>. This imaging modality has been recently used for assessment of ECV in healthy volun-



**Figure 4** The top left plot shows the time course of equilibrium state of iodinated contrast media distribution in the extracellular volume of the blood (dashed line), healthy myocardium (solid line) and skeletal muscle (dotted line) over the course of 10 min using multi-detector computed tomography. The plots also demonstrate the remarkable difference in myocardial extracellular volume (MECV) in regions subjected to different insults. Differential increase in ECV was observed in ischemic myocardium after microembolization using 16 mm<sup>3</sup> (top right), 32 mm<sup>3</sup> (bottom left) or 90 min left anterior descending coronary artery occlusion/reperfusion (bottom right) compared with undamaged remote myocardium in all groups (dotted lines). MDCT: Multi-detector computed tomography.



**Figure 5** Delayed contrast enhanced magnetic resonance imaging of acute reperfused myocardial infarction (3 d) showing the hyperenhanced infarct and microvascular obstruction (arrows).

teers<sup>[60]</sup> and infarcted swine hearts<sup>[61]</sup>. Investigators found on MDCT that the ECV in healthy volunteers is between 23%-26%<sup>[62,63]</sup>. We found in swine model of AMI that the ECV of iodinated contrast media is 24% in normal and 68% in infarcted myocardium (Table 1). Furthermore, the distribution volume of iodinated contrast medium was lower at the peri-infarct zone than infarct, suggesting that this zone contains admixture of viable and nonviable myocardial cells. In chronic infarct, the ECV in remote undamaged myocardium decreased to 18% as a result of compensatory hypertrophy (Table 1). Schelbert *et al*<sup>[29]</sup> and Schmidt *et al*<sup>[64]</sup> also observed extensive heterogeneity

in scar infarct, derangement in myocardial structure and accumulation of interstitial collagen that alters electrical activity and stiffens the myocardium. A clinical study showed that microvascular obstruction (MVO) occurs in > 30% of patients after ST segment elevation in myocardial infarction<sup>[65]</sup>. The presence of MVO in the infarct is problematic in the assessment of ECV, because the rate of contrast wash-in and wash-out is severely reduced in MVO zone and the equilibrium state condition takes 18 min post contrast injection<sup>[56]</sup>. Furthermore, the signal intensity of MVO zone is similar to remote undamaged myocardium (Figure 5).

**Table 1** Multi-detector computed tomography quantification of extracellular volume in patchy microinfarct caused by microemboli, contiguous homogeneous infarct caused by left anterior descending coronary artery occlusion and remote undamaged myocardium

Intervention	Remote myocardium	Infarcted region
16 mm <sup>3</sup> and 3 d (AMI)	25 ± 4	33 ± 4 <sup>a</sup>
32 mm <sup>3</sup> and 3 d (AMI)	24 ± 2	40 ± 1 <sup>a,c</sup>
90 min LAD and 3 d (AMI)	24 ± 1	54 ± 4 <sup>a,e</sup>
90 min LAD and 5 wk (scar)	18 ± 2 <sup>b</sup>	68 ± 4 <sup>a,g</sup>

<sup>a</sup>*P* < 0.05 *vs* remote myocardium; <sup>c</sup>*P* < 0.05 *vs* 16 mm<sup>3</sup> microemboli volume; <sup>e</sup>*P* < 0.05 *vs* 32 mm<sup>3</sup> microemboli volume; <sup>b</sup>*P* < 0.05 *vs* 90 min coronary artery occlusion/reperfusion at 3 d. AMI: Acute myocardial infarct.

MRI has inherent challenges that can be summarized as follows: (1) the presence of dental prostheses, orthopedic hardware or LV assist devices in the scanner; (2) slow acquisition time associated with high cost; (3) unsuitable for claustrophobic or uncooperative patients; (4) high technical and personnel requirements; and (5) MR contrast media provides a non-linear relationship between signal intensity and concentration<sup>[66]</sup>. On the other hand, MDCT has the potential to accommodate a growing population of patients who are counter indicated for MRI. MDCT has different challenges such as: (1) presence of radiation exposure precludes serial assessment; (2) low contrast between infarct and normal myocardium; (3) requires post imaging reconstruction of images; and (4) lack of sequences analogous to MRI that provide circumferential/longitudinal LV strain data (such as tagging, phase contrast velocity encoded cine) or information on interstitial edema and hemorrhage (such as T2-weighted and T2\*-weighted imaging).

## SPECIFIC CARDIOMYOPATHY

Myocardial fibrosis (scar) can be related to either ischemic MI, non-ischemic cardiomyopathy, or the combination<sup>[67]</sup>. For example, diffuse and contiguous fibrosis has been reported in heart failure, aortic valve disease and hypertrophic cardiomyopathy<sup>[29,68-70]</sup>, while solely diffuse fibrosis has been observed in myocarditis, hypertrophic/dilated cardiomyopathy, amyloidosis, congenital heart disease, aortic stenosis, restrictive cardiomyopathy (hyper eosinophilic and idiopathic types), arrhythmogenic right ventricular dysplasia and hypertension.

## ISCHEMIC MI

T1 mapping has been widely used to assess non-ischemic cardiomyopathies. Recent studies show that this technique also has the potential to assess ischemic MI. Klein *et al.*<sup>[71]</sup> determined ECV in 11 patients with heart failure and found that the ECV is greater in the infarcted region (54% ± 1%) than remote myocardium (29% ± 2%). Ugander *et al.*<sup>[20]</sup> measured ECV in 126 patients with myocardial infarct and non-ischemic myocardial fibrosis and detected sub-clinical abnormalities in remote myocardium

using ECV measurements. They found that scar infarct has significantly higher ECV (51% ± 8%) than remote undamaged myocardium (27% ± 3%, *P* < 0.001, *n* = 36). In patients with non-ischemic cardiomyopathy, the ECV of atypically enhanced and remote myocardium were (37% ± 6% *vs* 26% ± 3%, *P* < 0.001, *n* = 30). They also observed in these patients that ECV of remote myocardium increased with the decrease of LV ejection fraction (*r* = -0.50, *P* = 0.02). A similar observation was reported in patients with heart failure<sup>[48]</sup>. It has been shown that beta-blockers and angiotensin-converting enzyme inhibitors reduce diffuse myocardial fibrosis in patients with heart failure and hypertensive heart disease, respectively<sup>[72,73]</sup>, thus early measurement of ECV in suspected heart patients holds great promise for future clinical applications.

Coronary microembolization secondary to atherosclerotic plaque rupture occurs in spontaneously in patients with unstable angina/acute coronary syndromes<sup>[74-76]</sup> and accidentally during coronary interventions<sup>[77-83]</sup> with pathophysiological consequences, such as contractile dysfunction, perfusion-contraction mismatch, arrhythmias, myocardial ischemia and microinfarction<sup>[84-87]</sup>. Clinical studies showed that revascularization of an occluded coronary artery, using PCI, coronary artery stents, or bypass grafting, causes visible and invisible patchy microinfarct<sup>[88-91]</sup>. Both DE-MDCT and DE-MRI show promise in detecting patchy microinfarct caused by relatively large volumes of microemboli in a swine model (Figures 6 and 7)<sup>[92-99]</sup>, while equilibrium contrast enhanced MDCT provides a quantitative estimation of ECV as a function of microemboli volumes and duration of coronary artery occlusion (Figure 8). Histologic examination reveals dislodged microemboli in blood vessels surrounded with microinfarct (Figure 9). Small particles cause MVO, patchy microinfarct<sup>[100]</sup>, delayed infarct healing<sup>[101]</sup>, perfusion deficits and disturbances in ECG signal conductivity<sup>[102,103]</sup>. ECV data derived from equilibrium contrast enhanced MDCT in a swine model are shown in Table 1.

## NON-ISCHEMIC HEART DISEASES

### Myocarditis

Myocarditis is the most frequent disease in patients with acute coronary syndrome and normal coronary arteries<sup>[104]</sup>. Acute myocarditis is associated with systemic viral disease<sup>[105,106]</sup>. At the early stage, there is myocardial injury/infarction, edema and regional/global LV dysfunction. On DE-MRI, myocardial injury is focal and located in the sub-epicardium and mid-myocardium (Figure 1). This method was also used for quantifying myocarditis<sup>[107,108]</sup>. Furthermore, T2-weighted MRI sequence was also useful in detecting acute myocarditis for detecting interstitial edema, as an integral part of the inflammatory response, in acute myocarditis. This non-invasive method is useful for patients with acute chest pain, positive serum troponin and angiographically normal coronary arteries<sup>[109,110]</sup>. Mahrholdt *et al.*<sup>[110]</sup> speculated that the differential enhancement in the early phase is related to myocardial necrosis, but in the late phase to scar tissue. The sensitivity

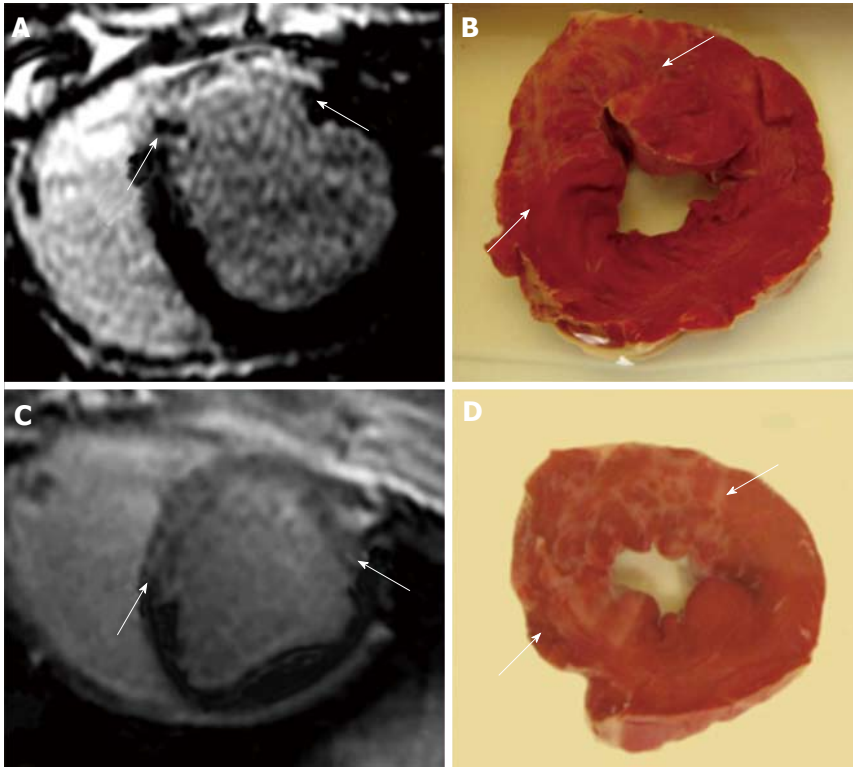


Figure 6 Delayed contrast enhanced magnetic resonance imaging (A and C) and histochemical triphenyltetrazolium chloride stain (B and D) show patchy microinfarct (arrows) 3 d after delivering 16 mm<sup>3</sup> (A and C) and 32 mm<sup>3</sup> (B and D) microemboli in the LAD coronary artery in a swine model.

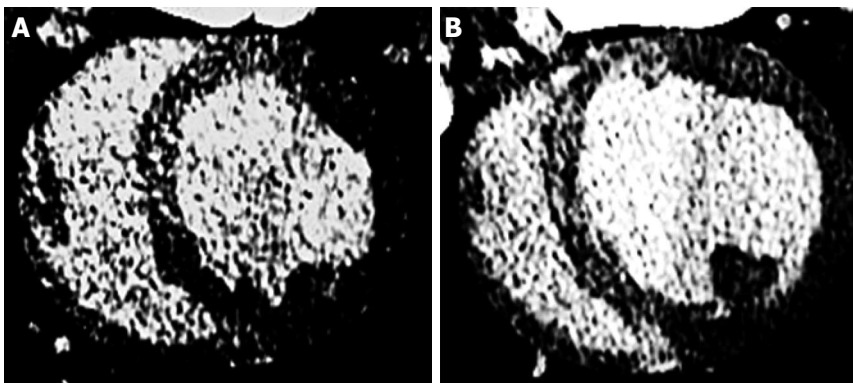


Figure 7 Delayed contrast enhanced multi-detector computed tomography 3 d after microembolization using 16 mm<sup>3</sup> (A) and 32 mm<sup>3</sup> (B) microemboli.

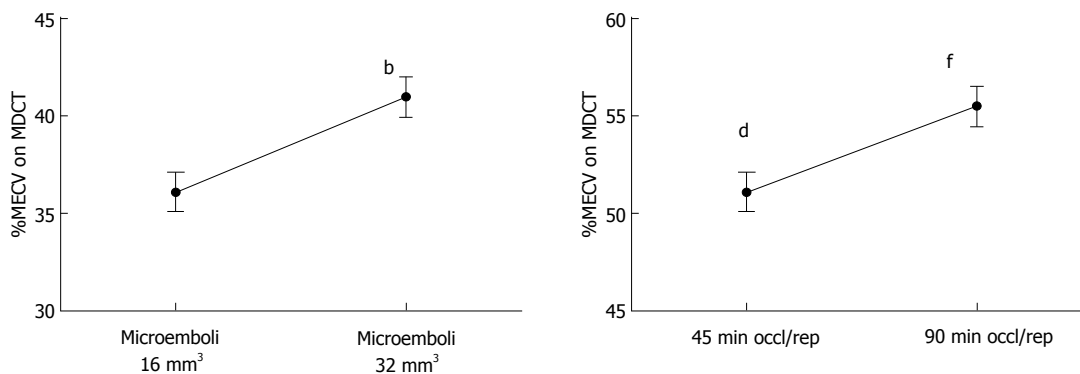
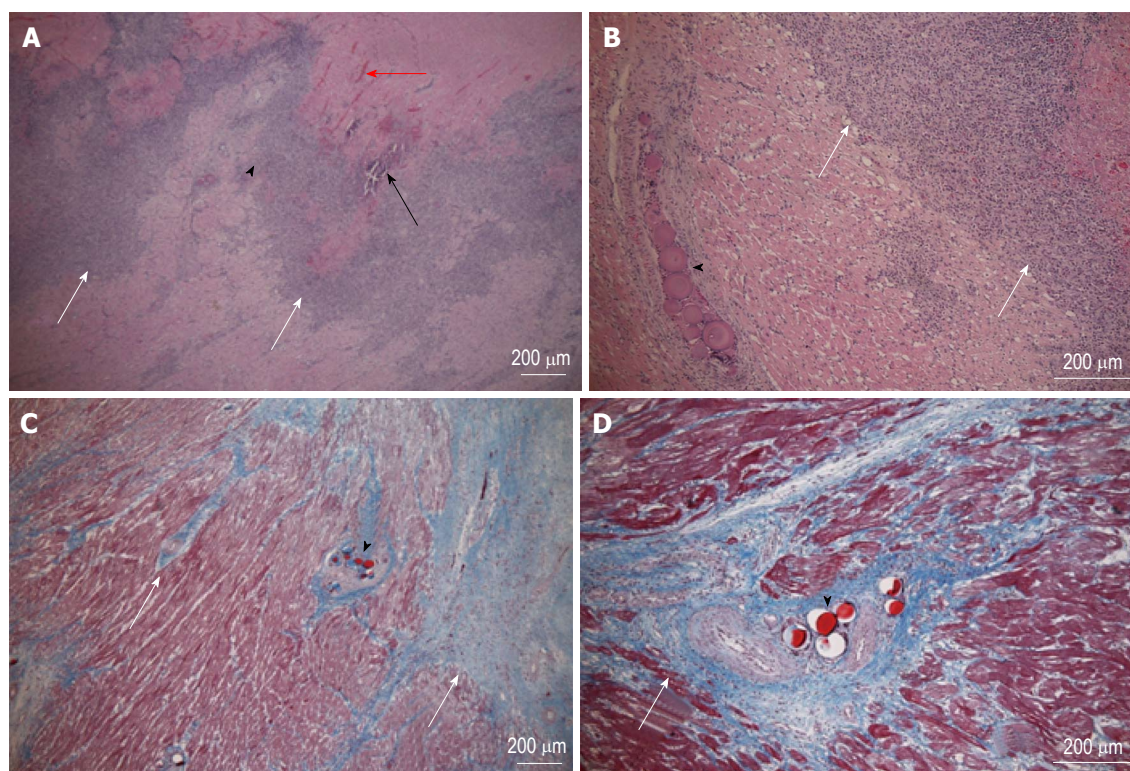


Figure 8 Gradient increase in myocardial extracellular volume as a function of microemboli volume (16 mm<sup>3</sup> vs 32 mm<sup>3</sup>) and left anterior descending coronary artery occlusion time (45 min vs 90 min). <sup>b</sup>*P* < 0.01 vs 16 mm<sup>3</sup>, <sup>d</sup>*P* < 0.01 vs 32 mm<sup>3</sup> and <sup>f</sup>*P* < 0.01 vs 45 min left anterior descending coronary artery occlusion/reperfusion. MECV: Myocardial extracellular volume; MDCT: Multi-detector computed tomography.





**Figure 9** Acute (top row, hematoxylin and eosin stain) and chronic (bottom row, Masson trichrome stain) patchy microinfarct (white arrows) and microemboli (black arrowhead) distribution between viable myocardium at 3 d and 5 wk after embolization, respectively. Intramyocardial hemorrhage (red arrow) and calcium deposition (black arrow) are evident at 3 d on HE stain, but not at 5 wk. The magnifications are 40 × (A and C) and 100 × (B and D).

of DE-MRI in detecting myocarditis has been variable because of the different patterns (diffuse *vs* focal and acute *vs* chronic) of enhancement<sup>[111-115]</sup>. More recently, Kellman *et al*<sup>[52,116]</sup> found that ECV is significantly higher ( $44\% \pm 6\%$ ) in myocarditic tissue compared with remote myocardium using T1 mapping.

### Hypertrophic cardiomyopathy

LV hypertrophy is an independent risk factor for sudden death<sup>[117,118]</sup>. Diffuse fibrosis is a common feature of hypertrophic cardiomyopathy and characterized by expansion of ECV and accumulation of interstitial collagen/fibrosis, which are hallmarks of pathologic remodeling<sup>[119]</sup>. Because ventricular hypertrophy prevalence estimates in the general population are as high as 16% the public health implications are significant<sup>[120]</sup>.

DE-MRI in hypertrophic cardiomyopathy showed that both diffuse fibrosis and necrosis share mid-myocardium and sub-epicardium of the ventricular septum<sup>[3,16,121,122]</sup> (Figure 1). Díez *et al*<sup>[123]</sup> provided evidence for the role of fibrotic remodeling in hypertensive heart disease. Myocardial fibrosis in ventricular hypertrophy can impair the electrical coupling of myocardial cells by separating these cells with collagen and create a substrate of tissue heterogeneity from which re-entrant arrhythmias may arise<sup>[124]</sup>.

Recently, Shiozaki *et al*<sup>[125]</sup> used MDCT to measure myocardial fibrosis in 26 patients with asymptomatic or mildly symptomatic hypertrophic cardiomyopathy. Myo-

cardial fibrosis was present in 25 of 26 patients (96%) with mean fibrosis mass of  $21 \pm 16$  g, while patients with appropriate implantable cardioverter defibrillator shocks for ventricular tachycardia/fibrillation had significantly greater myocardial fibrosis than patients without ( $29 \pm 19$  g *vs*  $14 \pm 8$  g;  $P = 0.01$ ). For a myocardial fibrosis mass of at least 18 g, sensitivity and specificity for appropriate implantable cardioverter defibrillator firing were 73% and 71%, respectively<sup>[125]</sup>.

Clinical studies showed that myocardial fibrosis is reversible and treatable with timely intervention, therefore early detection and assessment is crucial. Investigators proposed that ECV measured on MRI may be useful in serially assessing the effects of therapies focused on proliferation of fibrosis in myocardium, such as the ACE-inhibitor (lisinopril)<sup>[73]</sup> and the angiotensin II receptor antagonist losartan<sup>[73,123]</sup>. These therapies have been shown to reduce the LV wall stiffness and severity of myocardial fibrosis (measured on biopsy) and concomitantly improve diastolic function.

### DILATED CARDIOMYOPATHY

Dilated cardiomyopathy is an important cause of heart failure, sudden death and is the leading indication for cardiac transplantation in children and adults<sup>[126]</sup>. MRI provides accurate assessment of ventricular chamber size, wall thickness, and systolic function. The pattern of DE-MRI can differentiate ischemic *vs* non-ischemic heart dis-

ease<sup>[12]</sup>. For example, a sub-epicardial or mid-myocardial enhancement suggests non-ischemic cardiomyopathy. McCrohon *et al*<sup>[12]</sup> reported that specific patterns of enhancement have been purported in dilated cardiomyopathy to indicate a particular genetic association; however, these findings are nonspecific. Other investigators showed that 59% of patients with dilated cardiomyopathy and normal coronary arteries have no delayed enhancement. The other 28% of patients had mid-myocardial enhancement that is consistent with a non-ischemic cause and few patients had delayed endocardial enhancement that is consistent with ischemic cause. Others found in patients with dilated cardiomyopathy that the extent of fibrosis has been associated with increased risk of intraventricular systolic dyssynchrony<sup>[127]</sup>.

## CONGENITAL HEART DISEASE

Bandula *et al*<sup>[54]</sup> developed an equilibrium CT protocol, using iohexol at 300 mgI/mL delivered as a bolus of 1 mg/kg and a rate of 3 mL/s, followed immediately by an infusion of 1.88 mL/kg per hour with CT imaging before and at 25 min after injection of bolus of contrast agent. The ECV within the myocardial septum in 23 patients with severe aortic stenosis was measured using both equilibrium CT and equilibrium MRI in patients. Biopsy samples of the myocardial septum were collected during valve replacement surgery and used for histologic quantification of extracellular fibrosis. They found that the mean percentage of histologic fibrosis was 18% and a significant correlation between both equilibrium MDCT derived and equilibrium MRI derived ECV and percentage of histologic fibrosis ( $r = 0.71$ ,  $P < 0.001$  and  $r = 0.84$ <sup>[128]</sup>, respectively). Equilibrium MDCT derived ECV was well correlated to equilibrium MRI derived ECV ( $r = 0.73$ ). Broberg *et al*<sup>[33]</sup> also found the fibrosis index was significantly elevated in patients with congenital heart disease compared with normal controls ( $32\% \pm 5\%$  *vs*  $25\% \pm 2\%$ ;  $P = 0.001$ ), ECV values were highest in patients with a systemic right ventricle (L-transposition of the great arteries or D-transposition with prior atrial redirection surgery) and cyanosis ( $35\% \pm 6\%$ ;  $P < 0.001$  and  $34\% \pm 6\%$ ;  $P < 0.001$ , respectively).

Ho *et al*<sup>[129]</sup> were unable to visualize diffuse myocardial fibrosis in the setting of dilated cardiomyopathy using DE-MRI, but by T1 mapping technique, they found that fibrotic tissue has lower T1 relaxation time compared with healthy myocardium. Nacif *et al*<sup>[22]</sup> successfully measured interstitial myocardial fibrosis in hypertrophied hearts using ECV measurement method. Others found that ECV is higher in subjects with hypertrophic cardiomyopathy ( $36\% \pm 3\%$ ) than control volunteers ( $27\% \pm 1\%$ ,  $P < 0.001$ ). Furthermore, the ECV in hypertrophic hearts is heterogeneous and had substantially lower mean value than for scar infarct ( $69\% \pm 9\%$ ,  $P < 0.001$ )<sup>[116]</sup>.

Neilan *et al*<sup>[130]</sup> studied patients with hypertension and recurrent atrial fibrillation referred for pulmonary vein isolation underwent a contrast-enhanced MRI for measurement of ECV and were followed up prospectively

for a median of 18 mo. These patients had elevated LV volumes, LV mass, left atrial volumes, and increased ECV (patients with atrial fibrillation =  $34\% \pm 3\%$ ; healthy control volunteers =  $29\% \pm 3\%$ ;  $P < 0.001$ ). They found positive associations between ECV and left atrial volume ( $r = 0.46$ ,  $P < 0.01$ ) and LV mass, but negative association between ECV and diastolic function ( $r = -0.55$ ,  $P < 0.001$ ). Furthermore, they demonstrated that each 10% increase in ECV is associated with a 29% increased risk of recurrent atrial fibrillation and concluded that ECV was the strongest predictor of the primary outcome of recurrent atrial fibrillation and the secondary composite outcome of recurrent atrial fibrillation, heart failure admission, and death.

## AMYLOID

Amyloidosis refers to soluble proteins become insoluble, which are deposited in the extracellular compartment of various tissues, resulted in disrupting function<sup>[131]</sup>. Amyloid heart disease is a systemic infiltrative disorder<sup>[132]</sup>. It has been hypothesized that amyloidosis in myocardium is facilitated by hypoxia that results from capillary dysfunction. Endomyocardial biopsy has been considered to be the gold standard for demonstrating amyloid deposition in the heart. The most useful stain in the diagnosis of amyloid is Congo red, which, combined with polarized light, makes the amyloid proteins appear apple green on microscopy.

Noninvasive diagnosis of myocardial amyloidosis on MRI is difficult when this disease is accompanied with LV wall thickening related to hypertension<sup>[133]</sup>. Amyloid heart reveals small infarcted areas on unenhanced T1 and T2 MRI<sup>[134]</sup>. DE-MRI in myocardial amyloidosis is inherently challenging because amyloid infiltration within the extracellular compartment reduces the differences in contrast between LV chamber blood and myocardium such that the two regions may null simultaneously<sup>[133,135]</sup>. On the other hand, other investigators found that the appearance of global and subendocardial enhancement on DE-MRI, is a unique characteristic of cardiac amyloid and correlates with prognosis<sup>[136]</sup>. ECV was also measured in this disease using T1 mapping and gadolinium-based contrast media<sup>[34,137]</sup>. It was found that the median ECV is significantly higher in infiltrative diseases (49% of tissue volume) compared with non-amyloid cardiomyopathy patients (33%) and volunteers (24%). The ECV strongly correlated with visually assessed segmental DE-MRI ( $r = 0.80$ ) and LV mass index ( $r = 0.69$ ), reflecting severity of myocardial infiltration. Sado *et al*<sup>[35]</sup> reported that the ECV expansion is higher in systemic amyloidosis than in any other measured myocardial diseases, such as Anderson-Fabry disease, dilated cardiomyopathy, hypertrophic cardiomyopathy and hypertrophic cardiomyopathy, outside of the infarct zone. In another MRI study, Bandula *et al*<sup>[54]</sup> studied 40 healthy volunteers and 67 patients with systemic amyloid light-chain amyloidosis of the upper abdomen using equilibrium MRI. They found that ECV was measured in the liver, spleen, and paravertebral mus-



cle. ECV was highest in the spleen (34%), followed by liver (29%) and muscle (9%). In patients with amyloidosis ECVs measured within the spleen (39%), liver (31%), and muscle (16%) were significantly higher than in healthy controls.

## DIABETES

Type 2 diabetes mellitus promotes the expansion of ECV and increase vulnerability to a variety of clinical problems. Expansion of ECV is associated with mechanical dysfunction<sup>[138-140]</sup>, vasomotor dysfunction<sup>[141]</sup>, arrhythmia<sup>[142]</sup> and mortality<sup>[40,142]</sup>. Several studies support the notion that expansion of ECV contributes to adverse outcomes in diabetic patients. This notion is based on medications blocking the renin-angiotensin-aldosterone system ameliorate expansion of ECV<sup>[143-145]</sup>. In a recent study, Wong *et al.*<sup>[40]</sup> examined 1176 patients referred for MRI with and without diabetes. They found that diabetic patients ( $n = 231$ ) had higher median ECV than non-diabetic patients ( $n = 945$ ) (30.2% *vs* 28.1%,  $P < 0.001$ ). More importantly, expansion of ECV measured by MRI appeared to be ameliorated with medications blocking the renin-angiotensin-aldosterone system. They concluded that diabetes is associated with increased ECV, which may be an important intermediate phenotype in diabetic individuals that is detectable by MRI-ECV and could be used as a biomarker to follow the effectiveness of diabetic treatment.

The ability to distinguish the sub-endocardial, mid-myocardium or sub-epicardial regions with true pathophysiology is a major limitation of ECV measurement. The presence of intra-myocardial fat also affects ECV measurements. The other major limitations of non-invasive MRI and MDCT in measuring ECV are the quality of the acquired images, presence of microvascular obstruction (may require continuous contrast infusion to reach equilibrium state of distribution)<sup>[23,146]</sup> and the binding of contrast media to serum albumin that increases the relaxivity of some extracellular contrast media and decreases its diffusion<sup>[147]</sup>. ECV measurement or T1 mapping are not intended to replace DE-MRI or DE-MDCT, which are excellent at depicting large infarction, but rather to be used in concert with cine and perfusion techniques. In tissues with a large intravascular compartment (such as the liver), the values of ECV may be overestimated by the equilibrium technique. The noise in the MDCT images stemming from beam-hardening artifacts originating from dense vertebral endplates is another limitation. Potential technical improvements in ECV measurements include faster processing of image data that reduce reliance on expert interpretation and increase the speed of image data processing.

### Limitation

There are still multiple limitations in using MRI and MDCT for the assessment of ECV, such as the radiation dose, availability of experienced staff, extensive labor and the usage of contrast media. The side effects and cost of contrast media as well as costs of the scanner time

should be considered. Monitoring patients with severe heart failure or acute myocardial infarct inside the MR scanner is a difficult task.

## FUTURE APPLICATIONS OF ECV MEASUREMENTS

New drugs, transplantation of different stem cells and local injection of genes have been recently introduced as potential therapies for infarct healing and myocardial regeneration. Chronological estimation of ECV may be useful for documenting the effectiveness of these therapies to promote myocardial viability. Recent clinical and experimental studies have shown that stem cells reduce infarct size and improve LV function in both AMI and scar<sup>[148-151]</sup>. In a recent study Wong *et al.*<sup>[40]</sup> described an association between measurements of ECV and clinical outcomes in a large patient cohort undergoing MRI. They analyzed 793 patients with known or suspected coronary artery disease, cardiomyopathy, or arrhythmias. They excluded patients with cardiac amyloidosis, infiltrative disease, hypertrophic cardiomyopathy and areas of delayed contrast enhancement consistent with classic pattern of myocardial infarction. They found that ECV ranged from 22%-26% in healthy volunteers, whereas it ranged from 21%-46% in the patients. Over a median follow-up period of 6 mo, 39 patients died, and 43 experienced a major adverse event (composite of death/cardiac transplant/LV assist device implantation). In multivariable modeling, ECV was associated with adverse cardiac events. For every 3% increase in ECV, there was a 50% increased probability of an adverse cardiac event. Furthermore, the potential of MRI/MDCT in guiding intramyocardial therapies and providing reliable and reproducible assessment of myocardial viability, perfusion and function has been recently reviewed<sup>[152-154]</sup>. Further improvement in image resolution and processing of data would promise early detection and better pathophysiological understanding of diffuse fibrosis, myocardial infarct and help in timely intervention and therapy<sup>[155]</sup>.

In conclusion, since ischemic and non-ischemic myocardial diseases are characterized by an increase in the ECV, these pathologies can be characterized and may be differentiated on equilibrium contrast enhanced MRI/MDCT and T1 mapping. ECV data may provide a useful tool for diagnosis and treatment monitoring in ischemic and non-ischemic myocardial diseases (such as patchy microinfarct after percutaneous coronary intervention), compensatory hypertrophy, inflammation, heart failure and hypertrophic cardiomyopathy. The challenges lie in developing fast and sensitive imaging sequences, simple software for analysis, which will facilitate the ECV assessment approach into clinical routine practice.

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