Cardiac magnetic resonance assessment of diastolic dysfunction in acute coronary syndrome

Shah M. Azarisman1,2,3, Karen S Teo1,2, Matthew I Worthley1,2 and Stephen G Worthley1,2

Abstract
Chest pain is an important presenting symptom. However, few cases of chest pain are diagnosed as acute coronary syndrome (ACS) in the acute setting. This results in frequent inappropriate discharge and major delay in treatment for patients with underlying ACS. The conventional methods of assessing ACS, which include electrocardiography and serological markers of infarct, can take time to manifest. Recent studies have investigated more sensitive and specific imaging modalities that can be used. Diastolic dysfunction occurs early following coronary artery occlusion and its detection is useful in confirming the diagnosis, risk stratification, and prognosis post-ACS. Cardiac magnetic resonance provides a single imaging modality for comprehensive evaluation of chest pain in the acute setting. In particular, cardiac magnetic resonance has many imaging techniques that assess diastolic dysfunction post-coronary artery occlusion. Techniques such as measurement of left atrial size, mitral inflow, and mitral annular and pulmonary vein flow velocities with phase-contrast imaging enable general assessment of ventricular diastolic function. More novel imaging techniques, such as T2-weighted imaging for oedema, T1 mapping, and myocardial tagging, allow early determination of regional diastolic dysfunction and oedema. These findings may correspond to specific infarcted arteries that may be used to tailor eventual percutaneous coronary artery intervention.

1Cardiovascular Research Centre, Royal Adelaide Hospital, Adelaide, South Australia
2Department of Medicine, University of Adelaide, Adelaide, South Australia
3Department of Internal Medicine, International Islamic University Malaysia, Pahang, Malaysia

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Corresponding author:
Shah M Azarisman, Professor of Medicine, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, Bandar InderaMahkota, 25200 Kuantan, Pahang, Malaysia.
Email: risman1973@hotmail.com
Introduction
Chest pain is the most important presenting symptom of coronary artery disease (CAD). However, only 15%–20% of patients with chest pain are diagnosed with acute coronary syndrome (ACS) based on an electrocardiogram (ECG) and cardiac enzyme (CE) levels at presentation. This lack of diagnosis is predominantly due to the delay in pathophysiological manifestation of ACS, from arterial occlusion to overt ECG and/or a rise in CE. The consequences are manifold and up to 10% of patients with eventual myocardial infarction (MI) are misdiagnosed and inappropriately sent home. This also results in a major delay in treatment and inadequate risk stratification of patients, eventually resulting in progression to MI and/or complications arising from MI.

Therefore, there is an urgent need for a simple, but efficacious, investigative modality that enables rapid assessment, diagnosis, and risk stratification of ACS in patients presenting to the emergency department with chest pain. In the last 20 years, there has been an evolutionary shift in research and funding away from conventional investigations, such as ECG and CE measurement, towards cardiovascular imaging tools, such as echocardiography. More recently, computed tomography (CT)- and magnetic resonance imaging (MRI)-based investigative modalities have been used to diagnose ACS.

ACS
ACS refers to a variety of clinical presentations ranging from unstable angina to MI. These presentations result from underlying myocardial ischaemia subsequent to acute thrombosis induced by a ruptured coronary artery plaque. The main impediment to rapid and accurate assessment, diagnosis, and risk stratification of ACS is the apparent lag between coronary artery occlusion and manifestation of symptoms. This is complicated by the heterogeneous nature of the clinical presentation itself.

Within 10 to 20 seconds following coronary artery occlusion, the myocardial relaxation time begins to shorten, resulting in diastolic dysfunction and a rise in left ventricular (LV) end-diastolic pressure. Wall motion abnormalities then occur 15 to 30 seconds later, followed by a fall in LV ejection fraction. Subsequently, electrical signs and ischaemic symptoms may begin to manifest (Figure 1). However, these manifested symptoms are also dependent on the patients’ age, sex, and any underlying comorbidities, such as diabetes mellitus, which may delay and/or attenuate the symptoms.

The earliest detectable abnormality in ACS is either a reduction or cessation of coronary blood flow and altered myocardial perfusion. This has been the subject of many studies on the use of rest and/or stress myocardial perfusion imaging using single-photon emission CT, positron emission tomography, and cardiac magnetic resonance (CMR). These imaging modalities provide a high negative predictive value in patients with suspected ACS. Unfortunately, CT-based imaging techniques involve the use of radionuclide perfusion agents and the cost of setting up an acute perfusion imaging service in the emergency department is prohibitive. There is also a lack of sufficient diagnostic and prognostic data for greater use of CMR perfusion imaging in the emergency setting.
Diastolic dysfunction

Ventricular relaxation during diastole is an active process that is related to calcium uptake from contracted myocytes. Normal relaxation allows the left ventricle to fill at rest and during exercise without an increase in end-diastolic pressure. Diastolic dysfunction occurs when there is ischaemia-induced abnormality in LV relaxation and compliance. 15

Assessment of diastolic dysfunction post-ACS is important because it is correlated with infarct size, confers a higher risk of mortality, and is associated with a poorer prognosis, independent of LV systolic function. 16–19 Furthermore, in the acute setting, diastolic dysfunction portends a higher likelihood of progression to MI in the absence of any electrocardiographic or serological evidence of coronary artery occlusion, which occurs later in the temporal cascade of events. 14–16

The typical assessment modality for diastolic dysfunction is echocardiography. Echocardiography is usually performed prior to discharge to identify patients at higher risk of complications, and thus a poorer prognosis, to enable optimization of treatment. Therefore, although echocardiography is relatively inexpensive and easy to use, its use in the acute setting of assessment of ACS is limited. The main limitations to echocardiography are anatomical, reduced endocardial definition, inter-observer variability, and lack of tissue characterization.

An advantage of CMR is that it can potentially provide relevant incremental information during the acute assessment stage. CMR provides the possibility of accurately diagnosing ACS, eliminating potential differentials, and risk-stratifying patients with a single investigative modality. This in turn affects management and reduces time wastage, unwarranted referrals, and inappropriate discharge.

CMR imaging

In the emergency department, the difficulty in managing patients with chest pain is accurate early diagnosis and early, efficacious institution of treatment. CMR imaging offers high spatial resolution, enabling a detailed volume and functional assessment. Early diastolic dysfunction, which indicates the presence of
significant CAD, can then be coupled with late gadolinium enhancement imaging for excellent tissue characterization, and permits exceptional prognostic capacity. CMR techniques are able to provide a more accurate diagnosis of ACS compared with standard clinical assessment. Furthermore, the use of new imaging techniques, such as T2-weighted sequences for detection of oedema and T1 mapping, can be extended to patients with an intermediate to high risk for ACS.  

Assessment of diastolic function

Initial rest cine MRI uses steady-state free precession (SSFP) sequences to acquire a series of consecutive, breath-hold, long- and short-axis slices. These are used for assessment of ventricular wall motion, ventricular volume, ejection fraction, myocardial mass, and anatomy of extracardiac structures.

Left atrial size

The left atrium (LA) is directly affected by LV filling pressure and is a reliable indicator of the duration and severity of diastolic dysfunction. Chronic elevation in LV filling pressure results in LA dilatation and this is associated with an increased risk of death post-ACS. ACS may also affect atrial function by direct ischaemic injury. In the clinical setting, although LA volume is a better prognostic indicator, LA diameter and area are simpler to acquire, and thus easily measured.

The LA is visualized in the horizontal long-axis view (four-chamber view), at maximal size during end-systole, and just prior to opening of the mitral valve. Planimetry is performed by manually tracing the LA endocardial wall at end-systole of a cine sequence (SSFP) (Figure 2). The SSFP technique is used because it enables excellent contrast and good image quality. The LA is dilated when the planimetry area is greater than 24 cm².

Transmitral flow

Transmitral (TM) flow represents an immediate indicator of the filling gradient between the LA and LV. TM flow is normally assessed via transthoracic echocardiography (TTE), which records the filling pattern from which the degree of diastolic dysfunction is inferred. CMR uses through-plane, phase-contrast, velocity-encoded imaging to determine TM velocities.
Phase-contrast imaging is a validated technique for evaluating velocity, the velocity gradient, volume, and the pattern of blood flow.\textsuperscript{29,30} Although CMR-based phase-contrast imaging underestimates peak mitral E (early diastolic) and A (atrial contraction) velocities compared with TTE, the linear correlation between the two modalities is excellent.\textsuperscript{31–33}

To acquire cross-sectional TM flow, an imaging plane is planned parallel to the mitral annular plane at the level of the mitral leaflet tips from the LV outflow tract, vertical long-axis, or horizontal long-axis views (Figure 3). Phase-contrast, velocity-encoded data sets are then acquired with the velocity sensitivity set at 150 cm/s. A region of interest is manually drawn on one frame to encircle the cross-section of mitral valve (MV) leaflets as previously described.\textsuperscript{34,35} This is then propagated using a semi-automated contouring mode with manual override, yielding maximum velocity versus time graphs (Figure 3).

**Pulmonary vein flow**

Pulmonary venous (PV) flow wave form analysis is an important tool for evaluating LV diastolic function. The PV flow wave form is affected by LV filling and compliance, LA preload, and contractility.\textsuperscript{36} The main utility of measuring the PV wave form is that it is useful in differentiating between normal and pseudo-normal TM flow patterns.\textsuperscript{37,38}

Although there is no dedicated processing tool for PV flow, its wave form when compared with the TM flow pattern and LA area ensures optimal assessment of diastolic dysfunction in the acute setting. Furthermore, assessment of PV flow in CMR is almost guaranteed when compared with TTE assessment of PV flow. Assessment
of PV flow by TTE is only achievable in approximately 60% of cases because of anatomical and physical restrictions in attaining optimal views. Moreover, there is good correlation between TTE and CMR techniques for assessment of PV flow.34,37

Cross-sectional PV flow is acquired by placing an imaging plane 0.5 to 1 cm distal to the ostium, and perpendicular to the level of the right superior PV.39,40 A region of interest is then manually drawn on one frame to encircle the lumen of the PV and it is then propagated using a semi-automated contouring mode with manual override. This then yields the familiar velocity curve over time (Figure 4). Diastolic dysfunction can then be classified into four grades based on the E/A and S/D wave forms (Figure 5).

Myocardial tissue phase-contrast imaging

Tissue phase-contrast imaging is the CMR equivalent of TTE-based tissue Doppler imaging (TDI).41,42 Mitral annular velocity measurement by tissue phase-contrast imaging represents the rate of change in the LV
long-axis dimension and impaired relaxation results in a reduced early mitral annular velocity ($e'$). The ratio of early TM flow velocity (E) to early diastolic mitral annular velocity ($E/e'$) accurately predicts elevated LV filling pressure.\(^{42,43}\) An $E/e'$ ratio of $>15$ has been shown to be a strong predictor of decreased survival after acute ACS.\(^{44}\) CMR-derived $E/e'$ is also well correlated with TDI and pulmonary capillary wedge pressure measurements.\(^{39,45}\)

To acquire mitral annular velocity, an imaging plane is planned perpendicular to the LV base from the vertical long-axis and horizontal long-axis views. Phase-contrast, velocity-encoded data sets are then acquired with the velocity sensitivity set at 30 cm/s. A region of interest is manually drawn on one frame to encircle the inferiort septal basal region, which is then propagated, yielding maximum velocity versus time graphs (Figure 6).\(^{45}\)

**Myocardial tagging**

Myocardial tagging involves placement of a grid of radiofrequency tags on the myocardium, which then distorts with myocardial movement during systole and diastole.\(^{46,47}\) The deformation and displacement of these radiofrequency tags allows comprehensive analysis of diastolic strain and strain rate with good temporal and spatial resolution.\(^{48-50}\) The LV strain rate and torsion recovery rate directly reflect diastolic dysfunction. More importantly, myocardial tagging enables accurate assessment of regional diastolic dysfunction and has shown delayed infarction, hibernating myocardium, and transmural ischaemia.\(^{51}\)

Late gadolinium enhancement imaging is acquired via inversion-recovery segmented gradient echo T1-weighted sequences. Three sequential short-axis slices (basal, mid, and distal) are then obtained with six segments per slice corresponding to the coronary territory. Sequential grid-tagged images with identical slice positions are obtained using a two-dimensional turbo field-echo sequence with rest grid pulse for myocardial strain analyses, as previously described (Figure 7).\(^{49,52}\)

Harmonic phase analysis is used by placing a mesh around the epicardial and endocardial contours of the LV short-axis slices in each phase of the cardiac cycle (Figure 8). Lagrangian circumferential shortening strain is then computed, yielding...
time-strain curves (Figure 9). Peak diastolic strain (%) and strain rate (1/s) are then used for assessment of diastolic LV deformation.

**Future direction and prospects for clinical studies**

The use of phase-contrast imaging for flow assessment, myocardial tissue phase-contrast imaging, and myocardial tagging is gaining greater recognition and proving to be helpful for assessing of diastolic dysfunction by CMR. Moreover, detection of diastolic dysfunction in the setting of acute chest pain in patients with a moderate to high risk of CAD should indicate the need for further imaging sequences to adequately rule out CAD.

**Figure 6.** Cross-sectional mitral annular velocity measurement requires positioning of the sample plane perpendicular to the LV base in at least two orthogonal planes

**Figure 7.** Sequential grid-tagged images showing LV deformation during systole and diastole
Other novel imaging sequences include T2-weighted imaging for oedema or haemorrhage and T1 relaxation times with modified look-locker imaging. T2-weighted imaging using T2-short Tau inversion recovery (T2-STIR) is able to detect small changes in tissue composition of unbound intracellular water following an acute ischaemic event. These changes can be detected as early as 20 minutes following ischaemic injury and enable differentiation between acute and chronic myocardial infarcts compared with delayed gadolinium enhancement. T1 mapping allows accurate and reliable voxel-by-voxel mapping of infarcted myocardium. This obviates the need for delayed gadolinium enhancement and enables CMR use in patients who are otherwise contraindicated to gadolinium infusion. These two novel imaging

Figure 8. A mesh is placed around the epicardial and endocardial contours of the LV short-axis slices in each phase of the cardiac cycle
sequences, when paired with regional diastolic dysfunction assessment by myocardial tagging, may allow segment-by-segment evaluation of ischaemia in ACS and guide eventual percutaneous coronary intervention.

Patients presenting with ACS can undergo volume and functional assessment, T2-STIR for imaging of oedema, measurement of TM flow velocity for universal diastolic function, myocardial tagging for regional systolic and diastolic dysfunction, confirmatory first-pass myocardial perfusion assessment, and delayed gadolinium enhancement. These imaging modalities provide sufficient diagnostic and prognostic information for adequately assessing a patient presenting to the emergency department with chest pain and suspected of having ACS. These modalities take the same time that it takes to send and receive the results of any routine CE profile that is sent from the same department. Positive findings in any or a combination of these imaging modalities result in immediate referral for coronary intervention it is indicated. A negative finding results in immediate discharge from the emergency department, thereby reducing wastage and delay.

The main limitation to routine use of CMR imaging in ACS is the cost in terms of hardware and human resources. Additionally, newer imaging protocols may lengthen the scan time beyond what is acceptable for revascularization targets, and thus rule out the relevance of CMR in the emergency setting. Therefore, further research is required to establish the cost-effectiveness of CMR use in routine clinical practice.

Conclusion
Current clinical tools for comprehensive assessment of patients presenting to the emergency department with chest pain are useful, but not optimal. CMR imaging has the ability to accurately and reliably diagnose, risk stratify, and prognosticate ACS, especially with its multimodal ability to assess diastolic dysfunction. Despite the manifold benefits of CMR, its wider use in routine clinical assessment is limited, and more studies are required for assessing its cost-effectiveness.

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