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Imaging of the heart: historical perspective and recent advances

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ABSTRACT

Correct diagnosis must be made before appropriate treatment can be given. The aim of cardiac imaging is to establish cardiac diagnosis as accurate as possible and to avert unnecessary invasive procedures. There are many different modalities of cardiac imaging and each of them has advanced tremendously throughout the past decades. Echocardiography, as the first-line modality in most clinical circumstances, has progressed from two-dimensional, single-planed M-mode in the 1960s to three-dimensional speckle tracking echocardiography nowadays. Cardiac computed tomography angiogram (CCTA) has revolutionised the management of coronary artery disease as it allows clinicians to visualise the coronary arteries without performing an invasive angiogram. Because of the high negative predictive value, CCTA plays an important reassuring role in acute chest pain management. The greatest strength of cardiovascular magnetic resonance (CMR) is that it provides information in tissue characterization. It is the modality of choice in assessing myocardial viability and myocardial infiltration such as haemochromatosis or amyloidosis. Each of these modalities has its own strengths and limitations. In fact, they are complementing each other in different clinical settings. Cardiac imaging will continue to advance and, not long from now, we will not need invasive procedures to make an accurate cardiac diagnosis.

INTRODUCTION

Cardiac imaging has come a long way in the past 90 years. In 1925, when simple chest radiography was the only modality allowing clinicians to look at the heart, the size of the heart chambers was assessed by viewing the different silhouettes of the cardiac shadow. In 2015, not only are there many different advanced cardiovascular imaging modalities to choose from, but we can also accurately evaluate the heart both anatomically and functionally. Each of these imaging modalities (echocardiography, cardiovascular CT (CCT), cardiovascular MR (CMR), invasive coronary angiography, cardiac positron emission tomography (PET) and nuclear cardiology (NC)) has developed and advanced during the decades as described in this review.

ECHOCARDIOGRAPHY

As the first line dedicated cardiac imaging modality used nowadays in most clinical circumstances, transthoracic echocardiography (TTE) first came into clinical use in the early 1960s, although the discovery of the medico-diagnostic potential of sound waves can be traced back to the 17th century.[1] First generation TTE consisted only of M-mode, which produced print-outs of arrays of lines representing different cardiac structures in a single plane. The diagnosis of various cardiac conditions such as mitral stenosis, hypertrophic cardiomyopathy (HCM) and heart failure was based on the different M-mode patterns. In the early 1970s, the world's first two-dimensional (2D) TTE became commercially available. Further development in cardiac ultrasound has since progressed rapidly. Colour flow Doppler became available for heart valve assessment in the late 1970s; trans-oesophageal echocardiography (TOE) started to be developed around the same time. TOE was widely used in routine clinical practice in the early 1980s and allowed physicians to better visualise and evaluate the cardiac structures. Throughout the past three decades, TOE technology has progressed from single-plane transducers in the 1980s to multi-plane transducers in the 1990s to three-dimensional (3D) transducers. Indeed, 3D TOE has become an essential peri-procedural cardiac imaging modality in structural heart interventions such as trans-cutaneous aortic valve implantation (TAVI), mitral valve clipping and left atrial appendage occluder implantation. TTE continued to advance in the 1990s as tissue Doppler imaging (TDI) was first introduced to clinical practice. TDI assesses myocardial motion in relation to the transducer, at specific locations in the heart such as the septal mitral annulus. TDI has revolutionised echocardiographic diastolic function assessment as left ventricular filling pressure can be evaluated non-invasively using the E/e′ ratio. In 2000, Ommen *et al*[2] demonstrated a strong correlation between the E/e′ ratio and pulmonary capillary wedge pressure. They showed that E/e′ greater than 15 is associated with mean left ventricular diastolic pressure above 15 mm Hg (86% specificity; 64% positive predictive value). For the first time in the history of echocardiography, left atrial pressure, which is an important index for diastolic function, could be estimated non-invasively. This generated many research papers on diastolic heart failure.

With the introduction of 2D speckle tracking echocardiography (STE) in early 2000, myocardial mechanics could also be evaluated based on strain and strain rate.[3] Strain and strain rate are used to assess deformation of the myocardium and can be measured in different directions (longitudinal, radial, transverse and circumferential). Different forms of strain and strain rate have been proven to be useful in treating various cardiac conditions. For instance, longitudinal strain and strain rate are useful in identifying subtle ischaemic myocardial injury in acute coronary syndrome and early cardiotoxic effects from chemotherapeutic agents; radial strain and strain rate can be used in assessing

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mechanical left ventricular dyssynchrony in cardiomyopathy; and circumferential strain and strain rate are used in measuring myocardial torsion (twisting and untwisting). As with TOE, 3D TTE has become available in the past two decades. Much more compact 3D probes that generate 3D images with excellent spatial resolution have come on the market allowing 3D TTE.

As 2D TTE became well-accepted in clinical practice in the mid-1980s, stress echocardiography (both exercise and pharmacological) started to be used in investigating myocardial ischaemia.[4] Stress echocardiography became more accurate, while spatial and temporal resolution improved in the subsequent generations of ultrasound consoles in the following two decades.

Image quality has always been a big challenge in TTE and is very important for diagnostic accuracy. Thus, the development of contrast echocardiography was a major breakthrough in cardiac ultrasound.[5] Ultrasound contrast agents were first evaluated in the 1960s but were not widely recognised in clinical settings until 1996. These agents are gas-filled microbubbles and are most commonly used for left ventricular opacification (LVO) under low mechanical index imaging. With LVO, the accuracy of stress echocardiography was further improved and poor echogenicity was less of a limitation in patient selection for stress echocardiography. Myocardial contrast echocardiography with an ultrasound contrast agent can also be performed as an alternative to conventional stress echocardiography. There is on-going research on the therapeutic potential of contrast echocardiography.

As 3D and speckle tracking echocardiography continue to develop, myocardial strain and strain rate can now be measured in 3D. This novel echocardiographic technique is particularly useful in the assessment of cardiac mechanical dyssynchrony. The systolic dyssynchrony index (SDI), the degree of disparity of time to peak circumferential strain between myocardial segments derived by 3D STE, has been studied as a marker of LV mechanical dyssynchrony for cardiac resynchronisation therapy (CRT). Kapetanakis *et al* demonstrated that an SDI of 10.5% or above has very high predictive power for CRT response, whereas an SDI of 7.5% or less has very high predictive power for CRT non-response.[6] SDI is the first promising echocardiographic parameter for CRT patient selection since the PROSPECT trail, in which none of the 13 echocardiographic parameters was proven to be useful in predicting CRT responders.[7]

CARDIOVASCULAR CT

CCT was first introduced commercially as electron-beam CT (EBCT) in the early 1970s.[8] Although EBCT is not suitable for scanning moving organs, it remains an important imaging method to evaluate coronary calcification. Single-slice helical CT (SHCT) became available in clinical practice in 1996, substantially improving both spatial and temporal resolution, while gantry rotation times and slice thicknesses were reduced. When scanning at the steady phase of the cardiac cycle (70–80% of the RR interval) and a slow heart rate, SHCT can be used to assess coronary artery stenosis. Subsequently, CCT continued to develop into multi-detector CT (MDCT) with the 4-detector introduced in 1998, the 16-detector in 2001 and the 64-detector in 2004. The more the detectors, the shorter the gantry rotation times, and so temporal resolution is better and acquisition time is shorter. With 64-MDCT, the whole heart can be imaged in a single breath-hold and detailed coronary artery branches evaluated. Currently, 320-MDCT generates excellent image quality with a significantly lower effective radiation dose (4.4 mSv compared with 6.2 mSv with 64-MDCT). Other than increasing the number of detectors, another advanced technology to reduce radiation dose is dual source CT (DSCT) imaging. Instead of one X-ray tube as in conventional MDCT, DSCT has two X-ray tubes scanning simultaneously. As a result, temporal resolution is doubled, while acquisition time and radiation dose are reduced by half.

Advances in post-processing software play have also played an important role in reducing radiation dose in CCT. For instance, iterative reconstruction reduces signal noise without compromising spatial and contrast resolution. The hot topic in CCT now is a one-stop imaging modality that evaluates the coronary arteries both anatomically and functionally. This can be achieved with CCT perfusion[9] or CCT fractional flow reserve (FFR). The former has already been adopted into clinical routines in some institutes. Vendors have designed specific algorithms and software to quantify myocardial blood flow (MBF) and volume. However, although CCT-FFR has not yet been fully adopted, it has value in assessing the significance of coronary lesions. Both of these CT-driven functional tests will undoubtedly revolutionise cardiac imaging in terms of patient convenience.

Coronary artery calcium (CAC) score is a simple CT method to quantify the degree of coronary calcification. This is a very simple procedure with a very low radiation dose (approximately 1 mSv per study). Detrano *et al* demonstrated a very strong association between CAC and coronary events (myocardial infarction, death from coronary artery disease, definite angina followed by revascularisation, definite angina not followed by revascularisation, and probable angina followed by revascularisation).[10] In their study of more than 6000 patients of four different ethnicities with similar cardiovascular risk profiles, they showed that higher CAC scores carry a higher likelihood of coronary events. Because of the simplicity and safety of the CAC score, it is widely used as a cardiovascular screening test in many countries.

A further major player in CCT is coronary CT angiography (CCTA) which has a very high negative predictive value and specificity. Because of this characteristic, CCTA is an ideal tool to rule out significant coronary artery disease in patients with chest pain and intermediate pre-test probability. This is particularly useful in the accident and emergency department (AED). Litt *et al*[11] analysed 1370 low-to-intermediate risk patients with chest pain who were randomised into a CCTA-based strategy and a traditional strategy (stress tests with or without imaging). They demonstrated that CCTA was a safe alternative to exclude significant coronary artery disease, and that it also shortens length of stay in the AED and reduces unnecessary admissions. Priest *et al* have demonstrated that a CCTA-based strategy (CCTA then SPECT) is more cost-effective than a stress-based strategy (ECG, SPECT and TTE) due to a reduced hospitalisation rate.[12] As mentioned above, ongoing research on the feasibility and reliability of functional assessment of myocardial ischaemia with either CCT-perfusion or CCT-FFR will provide further insights into AED chest pain management.

CARDIOVASCULAR MR

CMR started to develop in the 1970s.[13 14] Medical utilisation of MR is based on the observation of magnetic polarity due to hydrogen nuclei spin, which was first described by Bloch and Purcell in 1946. Static cardiac imaging was first performed in 1981. Owing to the beating and breathing motions of the heart, motion artefacts were a big challenge in dynamic cardiac imaging until the introduction of ECG-gated imaging in 1983. The following year saw the first clinical utilisation of phase-encoded imaging for blood flow and early investigation of the use of gadolinium-enhanced CMR. The application of steady state free precession (SSFP) was first described in 1986. Pharmacological stress CMR with dobutamine and dipyridamole entered clinical practice in the early 1990s. Tissue characterisation became feasible with the use of different imaging sequences and gadolinium. As CMR technology continued to progress, more advanced CMR utilisations such as short-tau inversion recovery imaging, free-breathing SSFP imaging, T1 and T2 mapping, tagging and diffusion tensor imaging emerged (figures 1–6).

Gadolinium is commonly used for CMR but the potential side effect of nephrogenic systemic fibrosis (NSF) is always of concern. The most important development in gadolinium contrast agents in the past decade has been the change from linear to macrocyclic gadolinium-based contrast agents. Macrocyclic agents bind the gadolinium molecules tighter and are, therefore, thought to be more stable and less likely to cause NSF.[15]

CMR plays an essential role in the field of cardiomyopathy and coronary artery disease. Prasad *et al* have published extensively on the diagnostic and prognostic value of CMR in non-ischaemic cardiomyopathy.[16–18] CMR is extremely useful in differentiating non-ischaemic cardiomyopathy from ischaemic cardiomyopathy based on the late gadolinium patterns. In non-ischaemic cardiomyopathy, late gadolinium enhancement (LGE) is usually confined to intramural distribution, while ischaemic cardiomyopathy has typical infarction-related subendocardial or transmural LGE. As a result, CMR greatly contributed to the management of troponin-positive chest pain as myocarditis and acute coronary syndrome give rise to very different appearances in T2-weighted and gadolinium imaging. As CMR is the gold standard for myocardial assessment, based on the pattern of left ventricular hypertrophy together with LGE distribution, hypertensive heart disease and HCM can be clearly differentiated in most clinical circumstances. The diagnosis of cardiac amyloidosis can also be confidently established with the use of CMR as amyloid-infiltrated myocardium has completely different gadolinium kinetics from that of normal myocardium. Even rare conditions such as Fabry disease can be diagnosed with high diagnostic confidence using CMR.

The right ventricle (RV) is notoriously difficult to evaluate by echocardiography due to its crescentic geometry and high tendency of signal dropout. With CMR, RV volume and ejection fraction can be accurately measured. The morphology of the RV can be thoroughly assessed, which is particularly important in diagnosing arrhythmogenic right ventricular cardiomyopathy (ARVC), a hereditary life-threatening condition. Important features of ARVC such as RV dilatation and free wall microaneurysm formation can be identified by CMR.

CMR has important prognostic value in various cardiac conditions. HCM is the most common cause of sudden cardiac death (SCD). The presence of myocardial fibrosis has been shown to carry a worse clinical prognosis in HCM. HCM patients with LGE on CMR have a higher occurrence of ventricular arrhythmia both at rest and during exercise. They also have a higher incidence of new atrial fibrillation and systolic dysfunction. On the other hand, HCM patients without LGE have an excellent clinical prognosis. Dilated cardiomyopathy (DCM) has been one of the most frequent indications for cardiac transplantation. In over 50% of such cases, no apparent aetiology is identified. Familial DCM with a strong genetic component accounts for about 20–30% of cases. DCM patients with LGE are at much higher risk of heart failure admissions, ventricular arrhythmia and SCD.

CMR can also provide important prognostic information in coronary artery disease. Myocardial viability, in term of contractility recovery after revascularisation, can be assessed based on the transmurality of an infarct on gadolinium-enhanced

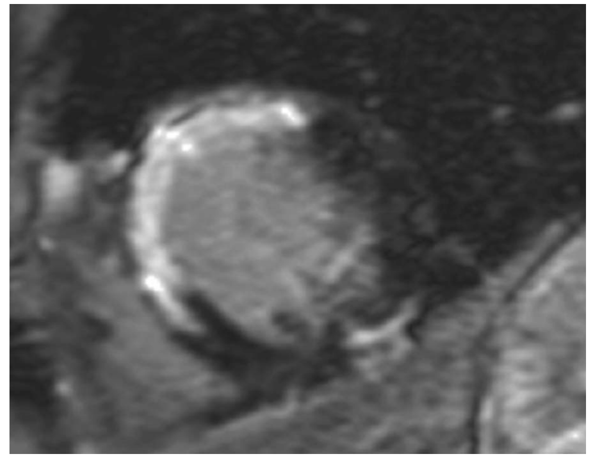

Figure 2 Transmural late gadolinium enhancement in the anterior and anteroseptal walls, which represents full thickness infarction.

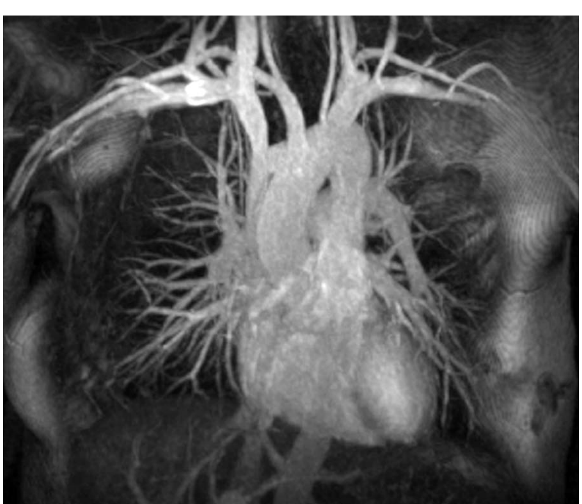

Figure 1 Contrast-enhanced MR angiogram in a normal subject.

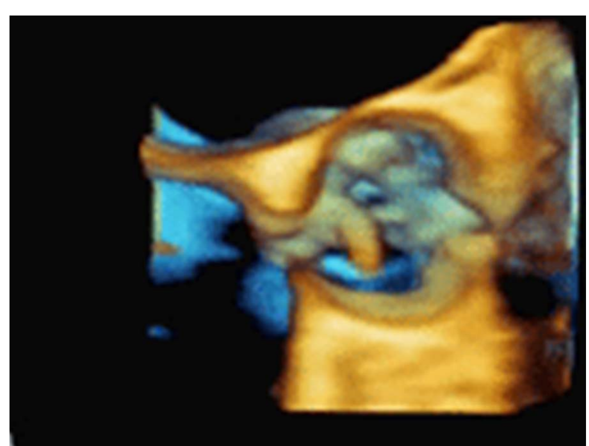

Figure 3 3D Trans-oesophageal echocardiography during trans-cutaneous aortic valve implantation: positioning of the guidewire across the aortic valve.

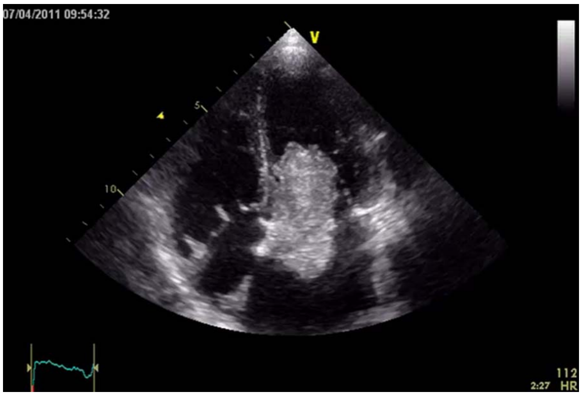

Figure 4 Large left atrial myxoma on transthoracic echocardiography (four chamber view, arrowed).

CMR.[19] Kim *et al* showed that infarcts with less than 50% transmurality have a much higher probability of post-revascularisation contractility recovery than those with transmurality greater than 50%. In clinical practice today, an infarcted myocardium with LGE transmurality of 75% or above is considered to be non-viable.

Finally, CMR allows cardiac iron loading to be estimated non-invasively. Iron-loaded myocardium and normal myocardium have very different T1, T2 and T2* relaxation times under MRI. Anderson *et al*[20] demonstrated a strong inverse correlation between liver T2* and biopsy-derived hepatic iron concentrations in thalassaemia major patients. In the same cohort, cardiac T2* correlates well with LV dilatation and LV dysfunction and considerably better than with serum ferritin or liver iron concentration. Tanner *et al*[21] have shown that T2* is an ideal and reliable method to monitor the cardiac efficacy of iron-chelating therapy. Furthermore, cardiac T2* also carries prognostic value in thalassaemia major patients. Kirk *et al*[22] demonstrated that shorter cardiac T2* (more severe myocardial siderosis) is associated with a higher risk of arrhythmia and heart failure. CMR (particularly with T2*) has contributed tremendously to the management of thalassaemia major patients, with the death rate falling dramatically in countries where T2* CMR has been adopted.

There is much current research on different aspects of CMR. First, tissue characterisation is no longer confined to gadolinium-enhanced imaging. As different tissues have different T1 and T2 relaxation times, by mapping the T1 relaxation times of the myocardium, AL cardiac amyloidosis can be diagnosed with high diagnostic accuracy.[23] Second, as it is radiation-free with excellent 3D capability, CMR has been gradually incorporated into cardiac interventions. It is particularly useful in paediatric vascular interventions, adult congenital heart disease interventions and complex electrophysiological ablative interventions. Third, compressed sensing has significantly increased the feasibility of CMR. With this innovation, the whole heart can be scanned in just one single breath-hold (about 14 s). It produces images with good temporal and spatial resolution and its diagnostic accuracy is comparable to standard SSFP.[24] A compressed sensing sequence shortens the duration of a CMR study, which is beneficial for patients who have difficulties breath-holding and those whose conditions are too critical to allow them to be inside a scanner for long.

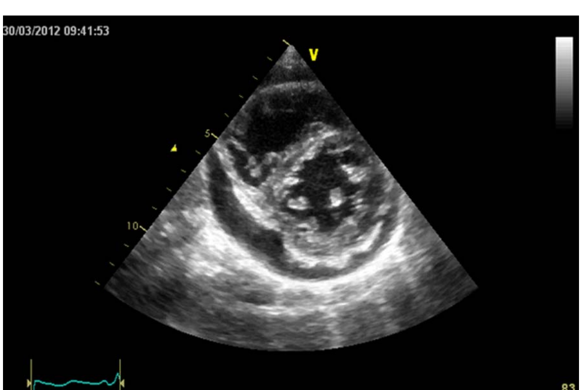

Figure 5 Pericardial effusion and pericardial metastasis on transthoracic echocardiography (parasternal short axis view, arrowed).

Figure 6 Multiple small plaques along the left anterior descending artery on CT coronary angiography.

NUCLEAR CARDIOLOGY

The concept of nuclear medicine first arose in late 1920s when radon gas in solution was injected in animal experiments in an attempt to kill cancer cells. However, NC was not widely used until 1972 when thallium-201 became commercially available and was used in myocardial perfusion imaging (MPI). At around the same time, the single-proton emission CT (SPECT) camera was invented. As the distribution and re-distribution properties of the tracers were determined, NC became important in assessing myocardial ischaemia and viability in the 1980s.

In recent years, a new generation of scanners has come on the market. The D-SPECT scanner is capable of completing an ECG-gated study in only 2 min, as opposed to 12–20 min with a conventional SPECT scanner. D-SPECT also generates better quality images, and so improves diagnostic accuracy.

Before the CMR era, cardiac PET imaging was regarded as the gold standard to assess myocardial viability.[25] The use of different radiotracers such as ^{82}rubidium and ^{18}F-fluorodeoxyglucose (FDG) allows MBF and myocardial metabolism, respectively, to be evaluated. Studies have shown that PET MPI generates significantly better image quality and diagnostic accuracy for identifying significant coronary stenosis (>50%) than SPECT MPI. Myocardial ischaemia can also be quantified by calculating the coronary flow reserve, the ratio of MBF at maximal vasodilation to MBF at rest. Myocardial viability assessment by PET depends largely upon changes in myocardial glucose and free fatty acid metabolism during ischaemia. Normal myocardial cells have high glucose uptake which decreases during ischaemia. By tracing the ^{18}FDG inside the myocardium, glucose utilisation and metabolism can be assessed. Combining the information obtained from ^{82}rubidium MPI and ^{18}FDG imaging, viable myocardium (preserved perfusion and glucose metabolism), non-viable myocardium (reduced perfusion and glucose metabolism) and, more importantly, hibernating myocardium (reduced perfusion with preserved glucose metabolism) can be differentiated. ^{18}FDG PET is considered to be the most sensitive tool to assess myocardial viability (sensitivity 91%). However, its cost, limited availability and radiation dose (about 12 mSv for a combined ^{82}Rb and ^{18}FDG scan) have precluded cardiac PET from being widely used in clinical practice.

Discussion on advances in non-invasive cardiac imaging would not be complete without mentioning advances in vasodilatory agents. MPI can now be done with almost all imaging modalities. For decades, the agent of choice was adenosine. However, with adenosine, adequate vasodilatory effect can only be achieved after several minutes of infusion. It also gives rise to many unpleasant symptoms such as chest discomfort, dyspnoea, facial flushing and headache. In 2008, a new selective adenosine 2A receptor agonist, regadenoson, became available. Its advantages over adenosine are that regadenoson is given as a fixed-dose single bolus and it has an improved side effect profile.[26] Regadenoson can be used safely in patients with asthma and bradyarrhythmia. Post-marketing studies have shown that regadenoson-MPI provides similar prognostic information to adenosine-MPI.[27]

CONCLUSION

A correct diagnosis is essential for correct treatment. In the field of cardiology, there are numerous new innovative therapeutic strategies, both mechanical and pharmacological. Cardiac imaging plays an extremely important role in establishing a diagnosis and guiding treatment. As the technology of different imaging modalities advances, more accurate and reproducible information can be provided to ensure patients receive the treatment they deserve.

Main messages

- The development in cardiac imaging has been enormous in the past 90 years.
- Echocardiography remains the mainstream first-line modality of cardiac imaging because of its availability and portability. It provides most of the essential clinical information in daily practice
- Cardiac computed tomography (CCT) has played an important role in chest pain management, particularly for patients with low risk and intermediate risk.
- Cardiovascular magnetic resonance (CMR) is the gold standard for ventricular volumes and mass evaluations. With the use of gadolinium, CMR is also a modality of choice to assess myocardial viability and infiltration.

Current research questions

- Is there a role of advanced echocardiography in predicting responses after cardiac resynchronisation therapy (CRT)?
- How accurate and reproducible of cardiac computed tomography (CT) perfusion and fractional flow rate (FFR)?
- In cardiovascular magnetic resonance (CMR), is tissue characterization by T1 and T2 mapping as robust as we think?

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Self assessment questions

Please answer true or false to the below statements,

1. Echocardiography can be used to estimate pulmonary capillary wedge pressure.
2. Ultrasound contrast is useful for left ventricular opacification under high mechanical index imaging.
3. High coronary calcium score associates with higher incidence of cardiac events.
4. New vasodilatory agent, Regadenoson, has better side effect profile than adenosine.
5. There is high chance of myocardial recovery after revascularization if the segment has 75% thickness late gadolinium enhancement on CMR.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

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Answers

1. True
2. False
3. True
4. True
5. False