Imaging

Myocardial ischaemia and viability: the pivotal role of echocardiography

Petros Nihoyannopoulos1,2* and Jean Louis Vanoverschelde3,4

1National Heart and Lung Institute, Imperial College School of Medicine, London, UK; 2Cardiology Department, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK; 3Pôle de Recherche Cardiovasculaire, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Belgium; and 4Division of Cardiology, Cliniques Universitaires Saint-Luc, Brussels, Belgium

Received 13 July 2010; revised 20 December 2010; accepted 6 January 2011; online publish-ahead-of-print 4 February 2011

Echocardiography has a central role for the diagnosis and management of patients with known or suspected coronary artery disease. Besides the fact that it provides an essential role in the differential diagnosis of patients presenting with chest pain in the emergency department, echocardiography provides a comprehensive non-invasive haemodynamic and functional assessment of those patients. Stress echocardiography in many institutions is now the preferred stress modality associated with imaging as it is cost-effective and does not use ionizing radiation. It is used for assessing patients with known or suspected coronary artery disease, risk stratification and for assessing myocardial viability. The recent introductions of ultrasound contrast agents as well as deformation imaging techniques have eliminated the last limitations of stress echocardiography such as image quality and quantification, respectively.

Keywords
Myocardial ischaemia • Echocardiography

Introduction

A lot has changed over the past 10 years in the world of echocardiography. The developments of other cardiac imaging modalities and in particular cardiac magnetic resonance imaging (cMR) and CT angiography provided a stimulus for the development of new sequences and modalities in echocardiography such as deformation imaging and three-dimensional echocardiography (3D-Echo). As a consequence, echocardiography has become a multimodality technique on its own rights. The widespread use of echocardiography has allowed for the collection of a large amount of outcome data so that today it is inconceivable for any patient with known or suspected coronary artery disease (CAD) not to have at least one echocardiographic examination. Finally, established training and a well-structured accreditation programmes provide the platform for regulating the practice of echocardiography.1–3

The distinction is made by rise in troponin levels in AMI but remain normal in ischaemia. Subarachnoid haemorrhage, acute pericarditis or myocarditis, hypertrophic cardiomyopathy, aortic dissection may all mimic acute coronary syndromes, with potential dire consequences as treatment for each of these conditions is fundamentally different. A potentially catastrophic scenario would be to give thrombolysis for suspected evolving AMI in a patient with aortic dissection or acute pericarditis. Conversely, not giving thrombolysis quickly enough in a patient with evolving AMI may condemn the patient to sustain extensive myocardial damage. While troponin levels are essential to diagnose AMI, those take several hours to become diagnostic. Echocardiography in the other hand can immediately differentiate the above conditions and provide the precise diagnosis, allowing for the appropriate and speedy intervention.

Acute chest pain syndroms

Differential diagnosis

Patients with acute chest pain often pose a diagnostic dilemma, as they can present with either acute myocardial infarction (AMI) with or without ST-segment elevation, or myocardial ischaemia.

Assessing resting left ventricle function in coronary artery disease

Global function

Although historically M-mode has been used to estimate left ventricle (LV) function, it has inherent flaws. It indeed only evaluates
the most proximal portion of the LV and ignores the most prognostically important LV regions, such as the anterior wall and apex. Consequently, in the setting of CAD, M-mode echocardiography should not be performed.

Two-dimensional echo is the reference technique to assess global LV function using the apical biplane method (Simpson’s). \(^4,^5\) Its main advantage is that it uses series of cross-sectional sections of the LV from base to apex, independent of shape and size. A second advantage is that all coronary vascular beds are evaluated so that the derived volumes provide accurate measurement of the global LV function. \(^6\) Finally, the large amount of outcome data from many clinical studies have established two-dimensional echocardiography (2D-Echo) as the mainstay technique for assessing LV function. One disadvantage, however, is that often the true cardiac apex is not fully visualized due to tangential cuts.

A prerequisite for accurate measurement of LV function is the ability to adequately visualize the endocardium. This is not always possible, particularly in the settings of coronary care or emergency units where the equipment used is not the most state-of-the-art. Suboptimal visualization and consequently measurement of LV volumes may lead to erroneous assessment of LV function, particularly when it is most needed, such as after an AMI. Although new transducer technologies and post-processing methods have improved image quality, there are still a number of patients in whom LV volumes cannot be evaluated. In these patients, it is recommended to use intravenous ultrasound contrast agents in order to improve endocardial border definition and consequently the accuracy of LV volumes measurements (Figure 1). \(^7,^8\)

The emergence of 3D-Echo adds to the accuracy of assessing LV volumes in a fast, semi-automatic fashion, and is not hampered by foreshortened views. \(^7\) Its accuracy was shown to be similar to that of cMR, \(^10,^11\) even in a multicentre setting with variable levels of experience. \(^12\) The addition of contrast can further optimize image acquisition and analysis. \(^13\) The recent introduction of single beat 3D-Echo makes this technique the current method of choice for the assessment of LV volumes. Progress is such that frame rates and image quality improve at galloping pace so that LV volume assessment by 3D-Echo will probably become the standard.

**Regional left ventricle function**

This requires the evaluation of all 16 segments of the LV according to the American and European guidelines. \(^5\) Those take into account all coronary vascular beds from at least one projection. The role of echocardiography in the detection of regional myocardial dysfunction is based on its ability to delineate myocardial thickness. During systole, a normally functioning myocardium thickens and moves towards the centre of the cavity. A typical segment can be 8–10 mm in diastole increasing by \(~50\)% during systole. Reduced systolic thickening in one or more myocardial regions will indicate reduced blood supply in this territory. The degree of hypokinesia may vary from minimal (hypokinesia) through severe (akinesia), up to paradoxical systolic expansion (dyskinesia). While assessing regional LV function is largely qualitative, it is possible to semi-quantify this using a 4-point scale from normal (grade 1) to dyskinetic (grade 4). The sum of the individual segment scores gives the wall motion score (WMS), which is used to assess severity of LV dysfunction. Dividing the WMS by the number of segments assessed gives the WMS index, which has been shown to be an important prognostic indicator. \(^14\) New quantitative methods for evaluating myocardial performance have emerged taking in consideration the direction of myocardial fibre architecture. Strain or strain rate (the rate of deformation over time) is derived from a high frame rate Tissue Doppler Imaging and measure myocardial deformation and contractility. \(^15,^16\) These modalities were introduced in order to overcome tethering of abnormal myocardial segment by adjacent normal segments and

---

**Figure 1** Apical four-chamber two-chamber and three-chamber projections from a patient with sub-optimal endocardial visualization (top) improving dramatically after 0.3 mg of sonovue contrast injection (bottom).
Detecting myocardial ischaemia

Pathophysiology

There is a well-established parallel relationship between regional coronary blood flow and contractile function in the corresponding territory.18,19 In patients with normal coronary arteries, myocardial blood flow (MBF) can increase >3-fold when oxygen demand increases, such as during exercise or inotropic stimulation using dobutamine stress, to allow for the increased heart rate and wall motion thickening (contractile reserve).

In patients with a significant coronary artery stenosis (>70%), resting MBF usually remains normal, as coronary resistances automatically decrease to compensate for the presence of the epicardial stenosis. Since part of the vasodilatory reserve is used for this purpose, the ability of MBF to increase when oxygen demand increases is less in the area subtended by a stenotic artery than in non-stenotic vascular beds. The concomittant decrease in distal coronary perfusion pressure leads to an absolute reduction in MBF in subendocardial layers, which in turn results in the hallmark of regional ischaemia, i.e. reduced in wall thickening (hypokinesia). When oxygen demand returns to normal (with exercise cessation), there is resolution of ischaemia with restoration of wall thickening.19

Acute coronary artery occlusion leads to a rapid reduction in resting MBF and hence cessation of muscular contraction in the area supplied. Relief of the occlusion, either spontaneously or by treatment (such as thrombolyis or PCI) allows regional wall function to recover back to normal. The duration and severity of myocardial ischaemia determines the severity of wall motion abnormalities (WMA) and the rate at which it recovers after the acute episode (‘stunned myocardium’).20

Stress echo for ischaemia

Myocardial ischaemia is accompanied by characteristic mechanical, electrical, and perfusion abnormalities. Although coronary angiography is the unequivocal reference method for the diagnosis of CAD, the anatomical description alone does not indicate the physiological significance of stenosis, stressing the need for a functional test. Exercise ECG, perfusion defects on single photon emission computed tomography (SPECT) or positron emission tomography (PET), and regional WMA on stress echocardiography or cMR, all permit assessment of the functional significance of coronary stenoses. The detection of regional LV dysfunction occurs early in the ‘ischaemic cascade’ preceding ECG changes and symptoms.

Echocardiography has by far the best spatial resolution (2 mm) over SPECT (12–15 mm) or PET (4 mm), only parallels that of CMR so that all myocardial regions can be visualized at rest and during stress. As a result, stress echocardiography has gained an unquestionable clinical role as an accurate and inexpensive stress test.21 With the most recent use of ultrasound contrast agents during stress, there is additional information provided by assessing myocardial perfusion.22,23

Specific markers of ischaemia

The presence of CAD does not automatically imply ischaemia, which is a dynamic phenomenon. For this, a functional test is preferred instead of just the anatomic detection of a stenotic lesion by either computed tomography or coronary angiography. Resting WMA alone may be indicative of a previous AMI, the age of which may be difficult to determine by echocardiography. Nevertheless, the detection of a substantial WMA (at least two contiguous segments) in a symptomatic patient may well point the diagnosis to the right direction.

Myocardial ischaemia can be detected in the following ways using echocardiography:

1. If normal resting wall motion, reduction in wall thickening of at least two contiguous segments during stress.
2. If resting akinesia (or hypokinesia) deteriorating during stress, both in extent (more segments) or in severity (from hypokinesia to akinesia).
3. If resting akinesia or hypokinesia that temporarily improves during low dose of dobutamine followed by subsequent deterioration at a higher dose. This implies that the myocardial segment is viable but subtented by a stenotic vessel and thus jeopardized.
4. A clear fall in overall LV function compared with baseline suggests extensive ischaemia. This may be evaluated by a fall in ejection fraction.
5. Using contrast ultrasound, the appearance of a perfusion defect during vasodilator stress or dobutamine. The perfusion
given intravenously starting from 5 to 40 mg established with long experience and good outcome data. Exercise associated ECG changes and symptoms. It is also well logical cardiovascular stress and that physicians are used to recognize.

The fundamental advantage of exercise is that it provides physiological cardiovascular stress and that physicians are used to recognize associated ECG changes and symptoms. Exercise echocardiography, like all imaging techniques, is operator dependent, both in respect of data acquisition and interpretation. Familiarity with all forms of stresses is an index of the quality of an echo laboratory. Indications for the individual patient can therefore be optimized, thereby avoiding the relative and absolute contraindications of each test. Proper training and experience is pivotal, as is for all imaging. The use of ultrasound contrast agents during stress echocardiography may also give additional information of myocardial perfusion. Following the ischemic cascade, hypoperfusion precedes WMA. Consequently, the addition of perfusion should be more sensitive than contraction alone. Myocardial contrast echocardiography (MCE) has been used to assess myocardial perfusion at rest and during stress. Low power imaging is the optimal mode for detecting myocardial perfusion and wall motion simultaneously. Two large prospective clinical studies showed the added value in diagnosing myocardial ischaemia when MCE was used to assess perfusion. They indicated that MCE significantly improves overall and regional sensitivity as well as negative predictive value for the diagnosis of CAD, when compared with wall motion assessment. Myocardial contrast echocardiography indeed allows perfusion abnormalities to be identified before WMA occur, thus improving sensitivity and accuracy in patients who fail to achieve the target heart rate, as well as in those in whom the test needs to be terminated prematurely.

The increasing availability of 3D-Echo may also allow for a better and easier assessment of LV function during stress. It has been shown to be equally accurate to 2D-Echo, but with much shorter acquisition times and greater reproducibility, owing to the use of the same transducer position throughout the examination. Although current 3D-systems provide relatively low frame-rates, the new equipment generation only requires a single heartbeat with higher frame rates, thus making stress 3D-Echo a clinical reality.

The combination of 3D-Echo with contrast is an attractive evolution of two of the most important recent developments in echocardiography. With contrast-enhanced 3D-Echo, LV volume measurements can be made fast, accurately and reproducibly, regional wall motion assessment is feasible for most LV segments, and perfusion defects can be assessed both at rest and during stress.

Methods of stress echocardiography

Exercise echocardiography

The fundamental advantage of exercise is that it provides physiological cardiovascular stress and that physicians are used to recognize associated ECG changes and symptoms. It is also well established with long experience and good outcome data. Exercise can be performed in either upright or supine positions, the latter being preferred when combined with echocardiography as it allows for the concomitant assessment of mitral or aortic valve function.

Dobutamine stress echocardiography

Dobutamine stress, which is easier to combine with echocardiography, has become the preferred method of stressing the heart in Europe, with similar diagnostic accuracy to exercise. Dobutamine is a synthetic catecholamine that stimulates primarily b1-adrenergic receptors with minimal b2 and a1 effects. It is given intravenously starting from 5 to 40 μg kg⁻¹ min⁻¹ in increments of 5 or 10 μg kg⁻¹ min⁻¹ for 3 min each. At low doses (<10 μg kg⁻¹ min⁻¹), it demonstrates a relatively more potent inotropic than the chronotropic effect, allowing stimulation of myocardial contractility before significant increases in the heart rate, and presumably ischemia, occur. At higher doses, both inotropic and chronotropic stimulation occur, resulting in increased cardiac output, myocardial oxygen consumption, and ischemia in myocardial regions subtended by significantly stenosed coronary arteries. Given intravenously, its half-life is ~2 min.

Dipyridamole stress echocardiography

Vasodilator stress with adenosine or dipyridamole induces MBF heterogeneity and ischemia. Dipyridamole (which provokes the accumulation of adenosine) stimulates adenosine receptors. In the presence of coronary stenosis, its administration causes a drop in post-stenotic pressure and therefore, a critical drop in subendocardial perfusion pressure, which in turn provokes a decrease in absolute subendocardial flow.

Feasibility

The perceived disadvantage of stress echocardiography is its inability to obtain optimal imaging in all patients. However, with the availability of ultrasound contrast agents, image quality is no longer an issue. The use of ultrasound contrast agents during stress echocardiography is now recommended by the European Association of Echocardiography when more than two contiguous segments are not well visualized.

Stress echocardiography, like all imaging techniques, is operator dependent, both in respect of data acquisition and interpretation. Familiarity with all forms of stresses is an index of the quality of an echo laboratory. Indications for the individual patient can therefore be optimized, thereby avoiding the relative and absolute contraindications of each test. Proper training and experience is pivotal, as is for all imaging. The use of ultrasound contrast agents during stress echocardiography may also give additional information of myocardial perfusion. Following the ischemic cascade, hypoperfusion precedes WMA. Consequently, the addition of perfusion should be more sensitive than contraction alone. Myocardial contrast echocardiography (MCE) has been used to assess myocardial perfusion at rest and during stress. Low power imaging is the optimal mode for detecting myocardial perfusion and wall motion simultaneously. Two large prospective clinical studies showed the added value in diagnosing myocardial ischemia when MCE was used to assess perfusion. They indicated that MCE significantly improves overall and regional sensitivity as well as negative predictive value for the diagnosis of CAD, when compared with wall motion assessment. Myocardial contrast echocardiography indeed allows perfusion abnormalities to be identified before WMA occur, thus improving sensitivity and accuracy in patients who fail to achieve the target heart rate, as well as in those in whom the test needs to be terminated prematurely.

The increasing availability of 3D-Echo may also allow for a better and easier assessment of LV function during stress. It has been shown to be equally accurate to 2D-Echo, but with much shorter acquisition times and greater reproducibility, owing to the use of the same transducer position throughout the examination. Although current 3D-systems provide relatively low frame-rates, the new equipment generation only requires a single heartbeat with higher frame rates, thus making stress 3D-Echo a clinical reality.

The combination of 3D-Echo with contrast is an attractive evolution of two of the most important recent developments in echocardiography. With contrast-enhanced 3D-Echo, LV volume measurements can be made fast, accurately and reproducibly, regional wall motion assessment is feasible for most LV segments, and perfusion defects can be assessed both at rest and during stress.
limitations. All those are set to assess the functional significance of a coronary lesion. Those modalities include stress echocardiography, MCE, SPECT, and cMR.

Table 1 compares the sensitivities and specificities for these various modalities derived in studies that have coronary angiography as a reference method. In general, these studies have shown that perfusion imaging had a somewhat better sensitivity but a somewhat lower specificity than techniques assessing regional wall motion. Interestingly, cMR has not shown to be superior to dobutamine stress echocardiography (DSE), despite claims of better image quality and reproducibility. These data indicate that whichever modality is preferred should not only be a matter of individual choice and local expertise but should also take into account any possible harmful effects for the patient, particularly irradiation. Most patients with chronic CAD will indeed need repeated coronary testing during the course of their disease and many will also require exposure to ionizing radiation as part of the workup of other intercurrent diseases. Accordingly, stress echocardiography and/or cMR should be preferred imaging modalities to assess CAD in these patients, the former having the advantage of being far more available.

Risk assessment and outcomes
Stress echocardiography can be used for screening high-risk patients before major peripheral vascular surgery or orthopaedic surgery, or in patients with chronic renal failure. Assessment of patients’ prognosis is important for cost-effective clinical decision making. A number of studies have demonstrated that the yearly event rate following a normal exercise or DSE is only 0.4–0.9%, a value not different from that seen following a normal SPECT. In a randomized controlled study in patients with suspected acute coronary syndrome and negative troponins, DSE resulted in less diagnostic uncertainty, fewer referrals for further investigations and a significant cost-benefit compared with exercise ECG.

In a landmark study, Poldermans et al. showed that the rate of cardiac death or myocardial infarction in patients with new WMA during DSE or extensive resting WMA increased 3.6- and 2.5-fold, respectively. In patients with extensive resting WMA or a left bundle branch block (LBBB), induction of new WMA increased the frequency of cardiac death or (re)infarction during a 5-year period from 12 to 31% and from 16 to 44%, respectively. They concluded that the risk of future cardiac events can be assessed by DSE, distinguishing subgroups of patient with high (>30% in 5 years), median (12% in 5 years), and low (8% in 5 years) risk. Importantly, patients with normal DSE have a good prognosis.

In the particular group of patients presenting with troponin negative acute chest pain syndrome, stress echocardiography was superior to exercise ECG in identifying patients with myocardial ischaemia. Similarly, in patients with new onset of chest pain and not previously known CAD, stress echocardiography provided an independent and incremental prediction of hard cardiac events beyond that provided by ECG and clinical data alone.

Finally, Rinkevich et al. convincingly demonstrated the advantages of early use of MCE in the emergency room. In a 2-year follow-up study in >1000 patients they showed that myocardial perfusion provides incremental prognostic value than regional function alone and that this is essentially confined to those with abnormal resting regional function. Those patients with abnormal regional function and normal myocardial perfusion fare better than those with both, abnormal function, and perfusion. The authors provide compelling evidence that contrast improves assessment of regional function.

Assessment of myocardial viability
Assessment of myocardial viability is another area in which echocardiography plays an important diagnostic role. It indeed allows for the assessment of two of the main features of myocardial viability, i.e. maintained resting perfusion and residual inotropic reserve.

Pathophysiology
Resting myocardial perfusion
Assessment of perfusion-contraction matching is crucial to the understanding of chronic LV ischaemic dysfunction. It requires the ability to measure regional MBF and to correlate these findings with data on regional myocardial function, acquired simultaneously. In clinical practice, this can only be achieved using PET and MCE. Resting flow measurements obtained in viable myocardium have been remarkably variable, about half of the segments showing reduced perfusion, the other half displaying...
only minor or no reductions in MBF. Viable myocardium encompasses a wide range of perfusion-contraction matching patterns, from perfusion-contraction mismatch, a characteristic feature of myocardial stunning, to moderate parallel reductions in perfusion and contraction (so-called myocardial hibernation).

**Myocardial flow reserve**
Irrespective of resting flow, perfusion reserve is always reduced in viable myocardium, albeit more severely in segments with low rest perfusion. The severity of flow reserve reduction directly impacts on contractile reserve, as this requires increases in MBF and oxygen consumption.

**Inotropic reserve**
Viable myocardium often displays contractile reserve when challenged by an inotropic stimulus, such as dobutamine or low level exercise. However, its response to these stimuli varies from segment to segment as well as with the intensity and the duration of stimulation.

Most viable segments exhibit a biphasic response when challenged by increasing levels of inotropic stimulation. At low levels, and provided that sufficient residual flow reserve is present, systolic wall thickening usually increases earlier in systole. At higher levels, when the increased in demand cannot be matched anymore by a further increase in MBF because of the underlying CAD, systolic function deteriorates and can even become worse than at baseline. The observation of such a biphasic pattern is extremely important to rule out other causes of regional dysfunction, like the presence of a subendocardial scar or the overall process of remodeling, in which a sustained contractile response at both low and high levels of inotropic stimulation is observed.

Not every viable segment improves during inotropic stimulation. About 25% of ‘metabolically’ viable segments, i.e. those with preserved energy metabolism, exhibit no contractile reserve. Compared with viable segments with recruitable contractile reserve, those lacking contractile reserve usually have a lower resting MBF and take up more glucose under fasting conditions than normal segments or viable segments with recruitable inotropic reserve, a finding consistent severely blunted myocardial flow reserve. Other factors also likely contribute to the lack of contractile reserve in otherwise viable segments, such as severity of the structural changes affecting the cardiomyocytes (vide infra) and the density and affinity of β-adrenoreceptors.

**Structural modifications**
Several structural alterations that affect the microcirculation, the cardiomyocytes and the extracellular matrix have been described in biopsy specimens harvested from viable segments in patients undergoing bypass surgery.

**Microcirculation**
The microvasculature is usually better preserved in viable than in non-viable segments. This is particularly true for the capillaries whose density is usually normal in viable segments but reduced, albeit to a variable extent, in non-viable segments. As would be expected, the major determinant of capillary density is the severity of interstitial fibrosis.

**Myocyte alterations**
The primary alteration seen in cardiomyocytes is the depletion of contractile elements. In some cells, this is limited to the vicinity of the nucleus, whereas in others it is very extended, leaving only few or no sarcomeres at the cell periphery. The space previously occupied by the myofilaments is filled with glycogen. Alterations in mitochondria, sarcoplasmic reticulum, T-tubules, and endoplasmic reticulum are also frequently noted. Many of the sarcomeric components are significantly reduced, whereas cytoskeletal proteins are usually disorganized. Gap junctions and the expression of connexin-43, a major gap junction protein, are also reduced.

**Extracellular matrix**
The interstitial alterations consist in increased amounts of type I collagen, type III collagen, and fibronectin. Within the widened interstitium are variable numbers of fibroblasts and macrophages, and scant increased amounts of elastic fibres. Importantly, acute ischaemic changes such as endothelial swelling of the microvasculature are absent.

**Animal models of myocardial hibernation**
Animal models of chronic coronary stenosis or progressive ameroind occlusion have shed a new light on both the mechanisms and the temporal progression of reversible ischaemic dysfunction. During the first weeks after the onset of dysfunction, endocardial MBF has been found to be either normal or only marginally decreased, implying that chronic myocardial stunning is the most likely mechanism of dysfunction. With time and probably also increases in the physiological significance of the underlying coronary narrowings, some of the dysfunctional segments which were ‘chronically stunned’ on early examination, eventually become underperfused. The transition from chronic stunning to chronic hibernation only occurs for threshold reductions in myocardial flow reserve. The experimental data thus suggest that chronic reversible myocardial ischaemic dysfunction is a complex, progressive, and dynamic phenomenon, that is initiated by repeated episodes of ischaemia, and in which resting perfusion, although initially preserved, may subsequently become reduced, probably in response to the decrease in myocyte energy demand.

**The pathophysiological spectrum of myocardial viability**
Altogether, the currently available data suggest that a spectrum of myocardial dysfunction exists in patients with coronary disease (Table 2). The initial stages of dysfunction most likely correspond to chronic stunning and are characterized by normal resting perfusion but reduced flow reserve, mild myocyte alterations, maintained membrane integrity (allowing the transport of cations and metabolic fuels), preserved capacity to respond to an inotropic stimulus and no or little tissue fibrosis. Following revascularization, functional recovery is likely to be rapid and complete. At the opposite, more advanced stages of dysfunction are probably associated with reduced rest perfusion, increased tissue fibrosis, more severe myocyte remodelling and a decreased ability to respond to inotropic stimuli. Nonetheless, membrane function and energy metabolism
long remain preserved. Following revascularization, functional recovery, if any, is usually delayed and in the end mostly incomplete (Figures 3–6).

**Role of echocardiography**

Echocardiography is probably the most versatile imaging modality for assessing myocardial viability. First, it readily identifies the core of the problem, i.e., the presence of regional WMA. It also allows one to assess their severity. Second, it allows for the initial characterization of the dysfunctional segments, both in terms of residual wall thickness and tissue reflectivity. Third, when combined with the use of ultrasonic contrast agents, it permits the assessment of MBF, both at rest and during hyperemia. Forth, when performed during an inotropic challenge, such as the infusion of increasing doses of dobutamine, it allows for the evaluation of the presence of recruitable inotropic reserve. And last but not least, it is the most frequently used technique to assess functional recovery after revascularization.

**Rest echocardiography**

Diastolic wall thickness measured during resting echocardiography provides some information on the relative amounts of myocardial tissue vs. fibrotic scar tissue within a particular myocardial segment. A diastolic wall thickness >6 mm has a sensitivity of 94% but a specificity of only 48% for predicting recovery of contractility after revascularization.63 The appeal of this method is its simplicity but it is limited by its poor specificity and the variability in the image quality which affects the accuracy and reproducibility of wall thickness measurements, as well as by the relatively small number of segments exhibiting reduced thickness.

Rest echocardiography and particularly contrast-enhanced 3D-Echo offers the opportunity to directly assess the amount and distribution of scar tissue. Indeed, myocardial scar tissue usually appears brighter than normal myocardium on diagnostic echocardiographic images, the intensity of the backscattered echo signals being proportionate to the amount, orientation, and compactness of the underlying collagen fibres. Although these areas of increased brightness can be readily seen on M-mode and 2D-Echo, a recent study has demonstrated that they could be more accurately localized and sized using 3D-Echo.64 These findings suggest that 3D-Echo could become an alternative to assess the amount of myocardial scar to cMR when cMR is either unavailable or contra-indicated.

**Myocardial contrast echocardiography**

The basic premise behind the use of MCE to assess myocardial viability is that only viable myocardium has an intact microcirculation. Earlier investigators used the intracoronary route for contrast administration. In both the immediate post-AMI setting or in patients with chronic dysfunction, MCE predicted recovery of LV function after revascularization with a high sensitivity (85–94%) and a lower specificity (43–65%). From these initial studies, MCE appeared to have similar test properties as thallium SPECT.65

With the development of new contrast ultrasound agents that can cross capillaries, and the introduction of newer contrast imaging modalities that reduce the microbubble destruction, MCE now allows essential parameters of the microcirculatory function, such as MBF and myocardial blood volume (MBV), to be measured. Measures of MBV by MCE correlate well with microvascular density and capillary area and inversely with collagen content.58 Myocardial blood flows have also been shown to be inversely correlated with collagen content. Yet, their relationship with microvascular density appears to be somewhat more complex. When microvascular density is reduced, MBF has usually been found to be reduced in proportion. Conversely, when the microvascular density is preserved, MBF can either be normal or reduced. Thus, whenever MBV is normal, assessment of MBF may help differentiate chronically stunned from truly hibernating myocardium. Accordingly, MCE predicts functional recovery with both a high sensitivity and a high negative predictive value (>90%). Specificity is somewhat lower (±65%), but better than with SPECT imaging.66

**Dobutamine stress echocardiography**

The demonstration of contractile reserve using various provocative stimuli, such as nitroglycerin, dipyridamole, postextrasystolic potentiation, catecholamines (e.g. isoprenaline, adrenaline, dopamine, or dobutamine), and exercise, can be studied with echocardiography. Dobutamine stress echocardiography is the most accepted and widely available of these techniques.

The protocol in most laboratories uses dobutamine infusion at two low-dose stages (5 and 10 \( \mu g \cdot kg^{-1} \cdot min^{-1} \)), with each stage lasting 3 min. Some advocate utilizing an even lower starting dose of 2.5 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) because in patients with critical coronary stenosis, myocardial ischaemia may be precipitated even with doses as low as 5 \( \mu g \cdot kg^{-1} \cdot min^{-1} \). Thereafter, the dose is increased in 10 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) increments to a maximum dose of 50 \( \mu g \cdot kg^{-1} \cdot min^{-1} \). Atropine may be given if the target heart rate is not achieved with standard dobutamine doses. The test is

<table>
<thead>
<tr>
<th>Table 2</th>
<th>The patterns of chronic ischaemic dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest flow</td>
</tr>
<tr>
<td>Chronic stunning</td>
<td>↔</td>
</tr>
<tr>
<td>Transition phase</td>
<td>↔</td>
</tr>
<tr>
<td>Chronic hibernation</td>
<td>↓</td>
</tr>
<tr>
<td>Infarction</td>
<td>↓</td>
</tr>
<tr>
<td>Remodelling</td>
<td>↔</td>
</tr>
</tbody>
</table>

P. Nihoyannopoulos and J.L. Vanoverschelde
**Figure 4** Inotropic response to dobutamine in dysfunctional segments (white arrows) with normal rest flow ($^{13}$NH$_3$) and F-18-fluorodeoxyglucose ($^{18}$FDG) uptake. The upper row shows images obtained from the apical four-chamber view in end-diastole at baseline and during the infusion of 5, 10, and 20 $\mu$g kg$^{-1}$ min$^{-1}$ of dobutamine. The lower row shows the corresponding end-systolic images. The yellow arrows indicate segments improving function, whereas red arrows indicate deteriorating segments. The sequence illustrates a typical biphasic response in the distal septum and the apex. Since blood flow and FDG uptake are normal in these segments, this is an example of chronically stunned myocardium.

**Figure 5** Inotropic response to dobutamine in dysfunctional segments (white arrows) with mildly reduced rest flow ($^{13}$NH$_3$) and a normal FDG uptake ($^{18}$FDG). The upper row shows images obtained from the apical two-chamber view in end-diastole at baseline and during the infusion of 5, 10, and 20 $\mu$g kg$^{-1}$ min$^{-1}$ of dobutamine. The lower row shows the corresponding end-systolic images. The yellow arrows indicate segments improving function, whereas red arrows indicate deteriorating segments. The sequence illustrates a very transient biphasic response in the mid-anterior segment, followed by immediate deterioration at the low heart rate. Since blood flow was slightly reduced and FDG uptake was normal in that segment, this is an example of mildly hibernating myocardium.
Figure 6 Inotropic response to dobutamine in dysfunctional segments (white arrows) with moderately reduced rest flow ($^{13}$NH$_3$) and a normal FDG uptake ($^{18}$FDG). The upper row shows images obtained from the parasternal long-axis view in end-diastole at baseline and during the infusion of 5 and 10 µg kg$^{-1}$ min$^{-1}$ of dobutamine. The lower row shows the corresponding end-systolic images. The sequence illustrates the absence of inotropic reserve in the anteroseptal segment. Since blood flow was definitively reduced and FDG uptake was normal in that segment, this is an example of severely hibernating myocardium.

Figure 7 Inotropic response to dobutamine in dysfunctional segments (white arrows) with severely reduced rest flow ($^{13}$NH$_3$) and FDG uptake ($^{18}$FDG). The upper row shows images obtained from the apical four-chamber view in end-diastole at baseline and during the infusion of 5, 10, and 40 µg kg$^{-1}$ min$^{-1}$ of dobutamine. The lower row shows the corresponding end-systolic images. The sequence shows the absence of inotropic reserve in the distal septum. Since blood flow and FDG uptake were both reduced in that segment, this is an example of irreversibly infarcted myocardium.
terminated when the patient achieves 85% of the age-predicted maximum heart rate or clinical or echocardiographic evidence of ischaemia occurs (Figure 7).

Most viable segments will demonstrate improvement of contractility at doses of 10 μg kg⁻¹ min⁻¹ or less. The benefit of proceeding to higher doses of dobutamine, even if contractile reserve is demonstrated at lower doses, is to observe the ‘biphasic response’. In the presence of significant coronary stenosis, an initial improvement in systolic wall thickening may occur at low doses of dobutamine, representing the region’s contractile reserve as previously stated. However, as oxygen consumption increases when contractility and the heart rate rise, the flow-limiting stenotic vessel is unable to keep up with the oxygen demand, and the ensuing ischaemia leads to hypokinesis of the affected wall segment. This biphasic response demonstrates two critical components to the definition of myocardial viability, namely viability itself and flow limitation. It is therefore not surprising if the biphasic response has the best predictive value of all the possible responses to dobutamine in determining improvement in LV function following revascularization. Accordingly, it is recommended to use the combined low- and high-dose approach in all patients who do not have contraindications.

The cumulative sensitivity, specificity, positive, and negative predictive values of DSE based on a recent meta-analysis were 81, 78, 75, and 83%, respectively. Although generally good, these figures imply that there are a significant number of false positive and false negative findings. False positive results can be partially explained by tethering of non-viable segments by adjacent normally contracting segments, leading to the illusion of improved function, by the presence of non-transmural infarction, by incomplete revascularization of otherwise viable segments and by the fact that functional recovery sometimes occur more slowly than allowed for by the follow-up periods. False negative findings are most often related to the fact that the myocardial flow reserve is reduced to such an extent that any increase in oxygen demand, even in viable segments, leads to ischaemia. Additionally, the ultrastructural changes occurring in viable myocardium may be so profound that contraction is not possible until sustained restoration of MBF has taken place. As with all stress echocardiographic techniques, wall motion scoring is limited by subjectivity and technical challenges. More objective assessment of regional wall function using myocardial deformation imaging should thus theoretically provide a better accuracy. However, a recent study using both tissue Doppler and Speckle tracking echocardiography did not show a significant advantage of these new methods when compared with the visual assessment of regional wall motion.

Dobutamine stress echocardiography also predicts prognosis in patients with chronic LV dysfunction. Several studies have demonstrated that long-term survival is better among patients with echocardiographic evidence of myocardial viability who had been revascularized than in those with either viable myocardium treated medically, non-viable myocardium undergoing revascularization, or non-viable myocardium treated medically. These data lend further support to the use of dobutamine echocardiography for the assessment of myocardial viability, as this technique not only allows accurate identification of which patient will improve its regional and global left ventricular function after coronary revascularization, but also may indicate those most likely to benefit with respect to prognosis.

Immediate post-infarction vs. chronic left ventricular dysfunction settings

The echocardiographic methods used to assess myocardial viability in the immediate post-infarction settings are similar to those in chronic LV dysfunction, i.e. assessment of residual myocardial perfusion, residual contractile reserve, and detection of inducible ischaemia. Several studies have demonstrated that the extent of regional perfusion and contractile reserve abnormalities correlated with the likelihood of spontaneous or post-revascularization recovery. After thrombolysis, observation of a biphasic response not only suggests the presence of viable myocardium but also indicates the persistence of significant residual stenosis on the infarct-related artery. One should nonetheless recognize that in the era of primary PCI, the interest in post-MI viability assessment has progressively been mollified, particularly whenever the infarct-related artery has been successfully treated.

Summary and conclusions

Echocardiography with its multiple modalities plays a central role in the evaluation of patients with known or suspected CAD, starting from the differential diagnosis of the patient presenting with acute chest pain. In the patient presenting with AMI, with or without ST-segment elevation, echocardiography is the first imaging modality to be used in order to ascertain the presence and extent of LV dysfunction and the presence of complications. In the absence of AMI, echocardiography will play an important diagnostic role to identify the presence of reversible myocardial ischaemia. Stress echocardiography in many institutions is now the preferred stress modality associated with imaging as it is cost-effective and does not use ionizing radiation. Finally, echocardiography plays a pivotal role in the assessment of myocardial viability since the presence and extent of viable myocardium may guide therapeutic strategies. It has been stressed that laboratories and individuals need to have experience and be accredited by the authorities so that the results of the range of echocardiographic investigations will be credible. Current and future developments, such as 3D-Echo and deformation imaging either with tissue Doppler of speckle tracking, hold the promise of making echocardiography even more quantitative, less operator-dependant and more reproducible than it is today. However, clinical studies are necessary to demonstrate their real clinical value.

Conflict of interest: none declared.

References


